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Mechanisms of reward in depression

An intervention study investigating the acute effects of lurasidone on cerebral blood flow and the neural correlates of reward and penalty processing

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**Mechanisms of reward in depression: An intervention study
investigating the acute effects of lurasidone on cerebral blood
flow and the neural correlates of reward and penalty
processing.**

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Abstract

Major Depressive Disorder (MDD) is a common, recurrent and disabling mental illness which is poorly treated by currently prescribed drug therapies. The discovery of treatment tools that target putative mechanisms of illness in depression is thus a clinical priority. Depression is characterised by hyporeactivity to reward and hyperactivity to aversive stimuli, which putatively reflects altered function in fronto-striatal-limbic brain regions innervated by monoamines. Yet, very few studies have used dopaminergic drugs to probe the association between neural reward- and especially penalty- signalling and depression. Such intervention designs are important for overcoming the limitations of correlational studies through randomization and experimental manipulation. Preliminary findings raise the intriguing possibility that dopamine antagonists with antidepressant properties may exert their effects via *reward* and/or *penalty* signal normalisation, however further studies are warranted. This thesis aims to address this knowledge gap by exploiting the advantages of a placebo-controlled design to examine how a novel D₂ antagonist with antidepressant properties, lurasidone, modifies activity in the brain's reward/penalty network in depression.

We recruited 43 medication-naïve participants across the range of depression severity (Beck's Depression Inventory –II score range: 0-43), including healthy volunteers, as well as people meeting full-criteria for MDD. In a double-blind placebo-controlled cross-over design, all subjects received either placebo or lurasidone (20mg) across two visits separated by one week. Functional magnetic resonance imaging (fMRI) with the Monetary Incentive Delay (MID) task assessed reward functions via neural responses during anticipation and receipt of gains and losses. The analyses focused on these two phases of reward processing as well as medication and depression effects on Prediction Error (PE), the brain's key dopaminergic learning signal encoding the difference between reward or loss outcome and their anticipation. We hypothesised that subjects scoring high on depression would show a baseline difference in fronto-striatal activity which would be reverted by acute-dose lurasidone. Moreover, we sought to address a key concern in pharmacoinaging studies, namely that shifts in global or regional CBF could underlie changes observed in BOLD fMRI signal. We therefore also used arterial spin labelling (ASL), an imaging modality that allows the quantification of cerebral blood flow at rest, to disentangle global and regional CBF

changes from BOLD fMRI signal. As such, this was the first investigation examining the acute effects of lurasidone in the human brain (across a spectrum of depression severity), on a well validated neuroimaging reward task, together with a concerted attempt to control for known potential confounds.

Our findings showed that lurasidone altered fronto-striatal activity during anticipation and outcome phases of the MID task without modification of behaviour. There was a significant three-way Medication-by-Depression severity-by-Outcome interaction in the anterior cingulate cortex (ACC) after correction for multiple comparisons. Follow up analyses revealed significantly higher ACC activation to *Penalty Outcomes* in high- versus low depression participants in the placebo condition, with a normalisation by lurasidone. We found an opposite pattern of signal normalisation for *Reward Outcomes* in the ACC and Nucleus Accumbens (NAcc). Lurasidone *enhanced* ACC and NAcc signalling to positive feedback in depressed individuals, however, this pattern did not remain significant after stringent correction for multiple ROI comparisons. Instead, we found that lurasidone significantly increased NAcc activation in individuals with higher symptoms of anhedonia. For the PE analyses, we found support for a normalisation in reward-related PE encoding in the amygdala and penalty-related PE encoding in the ACC in one of the three PE models tested. Finally, sensitivity analyses demonstrated that comorbid anxiety symptoms, self-reported changes in sedation and state anxiety and increased striatal CBF under lurasidone did not confound lurasidone's effects on reward and penalty processing in depression.

Taken together, an acute dose of lurasidone normalises (reduces) neural ACC responses to negative outcomes and PE encoding, without modification of behaviour in individuals with elevated depressive symptoms. Lurasidone also normalises (increases) striatal (NAcc) responses to positive feedback as a function of anhedonia severity. Potential mechanisms at the receptor level are discussed with reference to activity at Dopamine D₂ and Serotonin 5-HT_{1A}, 5-HT_{2A}, and 5-HT₇ receptors. The results provide evidence for abnormalities in neural reward-penalty systems in depression and highlight the potential of targeted pharmacological treatments to normalise penalty and reward-related processing in depression. The thesis brings increased knowledge and precision to our understanding of the effects of lurasidone, during different phases of reward and penalty processing across the continuum of depression and anhedonia severity.

Statement of work

This thesis used data from one study which was funded by the Wellcome Trust (093909/Z/10/A) and National Institute for Health Research (NIHR) Biomedical Research Centre (BRC) at South London and Maudsley NHS Foundation Trust and King's College London.

I was involved in all stages of the study: ethics, planning, recruitment, data collection, analysis and write up. Specifically, I contributed to the ethics application and amendments in collaboration with my supervisors and Dr. Nada Zahreddine. I led the planning and implementation of all study procedures (imaging protocol, design of the experimental paradigms, pharmacy (double-blinding and randomisation) with the aid of Dr. Fernando Zelaya, Alex Popescu and Rachel Barrett respectively). I had sole responsibility for participant recruitment, assessment and scanning sessions for all participants. I was also responsible for data pre-processing, analysis and writing up of the results under the supervision of and with the feedback from co-authors: Professor Mitul Mehta, Dr. Argyris Stringaris, Professor Allan Young, and Drs. Owen O'Daly, Fernando Zelaya, Nada Zahreddine, Ellen Leibenluft, Daniel Pine, Hanna Keren and Georgia O'Callaghan.

Preliminary results from this study were presented (via poster) at the American Academy of Child and Adolescent Psychiatry (AACAP) 63rd Annual Meeting, New York, NY, USA, Oct 24 - 29, 2016 and the International Society for Bipolar Disorders Annual Conference, Washington DC, USA, May 4-7, 2017 and the manuscript is currently under review.

The findings from this thesis are a direct product of my own work, with the supervision from Professor Mitul Mehta and Dr. Argyris Stringaris and feedback from co-authors. When referring to the methods and results included in this thesis, I use the third person ("we", "our") for consistency with the articles under submission.

Sections of the systematic review of depression and reward processing (Section 1.5) come from an article entitled "Reward processing in depression: a conceptual and meta-analytic review across electrophysiological and fMRI studies" (accepted by American Journal of Psychiatry journal, March 2018) , for which I am a co-author.

This thesis represents my own, original work. Where work has been derived from other sources, I confirm that this has been indicated within the thesis.

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Abbreviations

AAP	Atypical Antipsychotic
ACC	Anterior Cingulate Cortex
ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
APTD	Acute Phenylalanine and Tyrosine Depletion
ARI	Affective Reactivity Scale
ASL	Arterial Spin Labelling
BA	Behavioural Activation
BD	Bipolar Depression
BDI-II	Beck's Depression Inventory II
BOLD	Blood Oxygen Level Dependent
BP	Blood pressure
CBF	Cerebral Blood Flow
CBT	Cognitive Behavioural Therapy
CBV	Cerebral Blood Volume
CGT	Card Guessing Task
DA	Dopamine
DARS	Dimensional Anhedonia Rating Scale
DNRI	Dopamine Noradrenaline Reuptake Inhibitor
ECG	Electrocardiogram
EEG	Electroencephalography
FDR	Familial Depressive Risk
FGA	First Generation Antipsychotic
fMRI	Functional Magnetic Resonance Imaging
FWE	Family-wise Error
FWHM	Full Width Half Maximum
GAD	Generalised Anxiety Disorder
GLM	General Linear Model
HADS	Hospital Anxiety and depression Scale
HC	Healthy Control
HR	Heart Rate
IGT	Iowa Gambling Task
L-DOPA	L-3,4-Dihydroxyphenylalanine
MDD	Major Depressive Disorder
MEG	Magnetoencephalography
MFQ	Mood and Feelings Questionnaire
MID	Monetary Incentive Delay
MINI	Mini International Neuropsychiatric Interview
MNI	Montreal Neurological Institute
MPFC	Medial Prefrontal Cortex
MRI	Magnetic Resonance Imaging
N.s	not significant

NAcc	Nucleus Accumbens
NRI	Noradrenaline Reuptake inhibitors
OFC	Orbital Frontal Cortex
PE	Prediction Error
PET	Positron Emission Tomography
PFC	Prefrontal Cortex
phMRI	Pharmacological Magnetic Resonance Imaging
RCT	Randomised Control Trial
RDoC	Research Domain Criteria
ROI	Region of Interest
RSfMRI	Resting-state Functional Magnetic Resonance Imaging
sD	subthreshold Depression
SGA	Second Generation Antipsychotic
SHAPS	Snaith-Hamilton Pleasure Scale
SNRI	Serotonin and Noradrenaline Reuptake Inhibitors
SPM	Statistical Parametric Mapping
SSRI	Selective Serotonin Reuptake Inhibitors
SSRT	Stop Task
STAI-S	State trait Anxiety Inventory - State
TAP	Typical Antipsychotic
TCA	Tricyclic Antidepressant
UD	Unipolar Depression
VAS	Visual Analogue Scale
vlPFC	ventro lateral Prefrontal Cortex
vmPFC	ventro medial Prefrontal Cortex
VS	Ventral Striatum
WOF	Wheel of Fortune

Chapter 1 - Introduction

A map of the introduction chapter of this thesis is illustrated below.

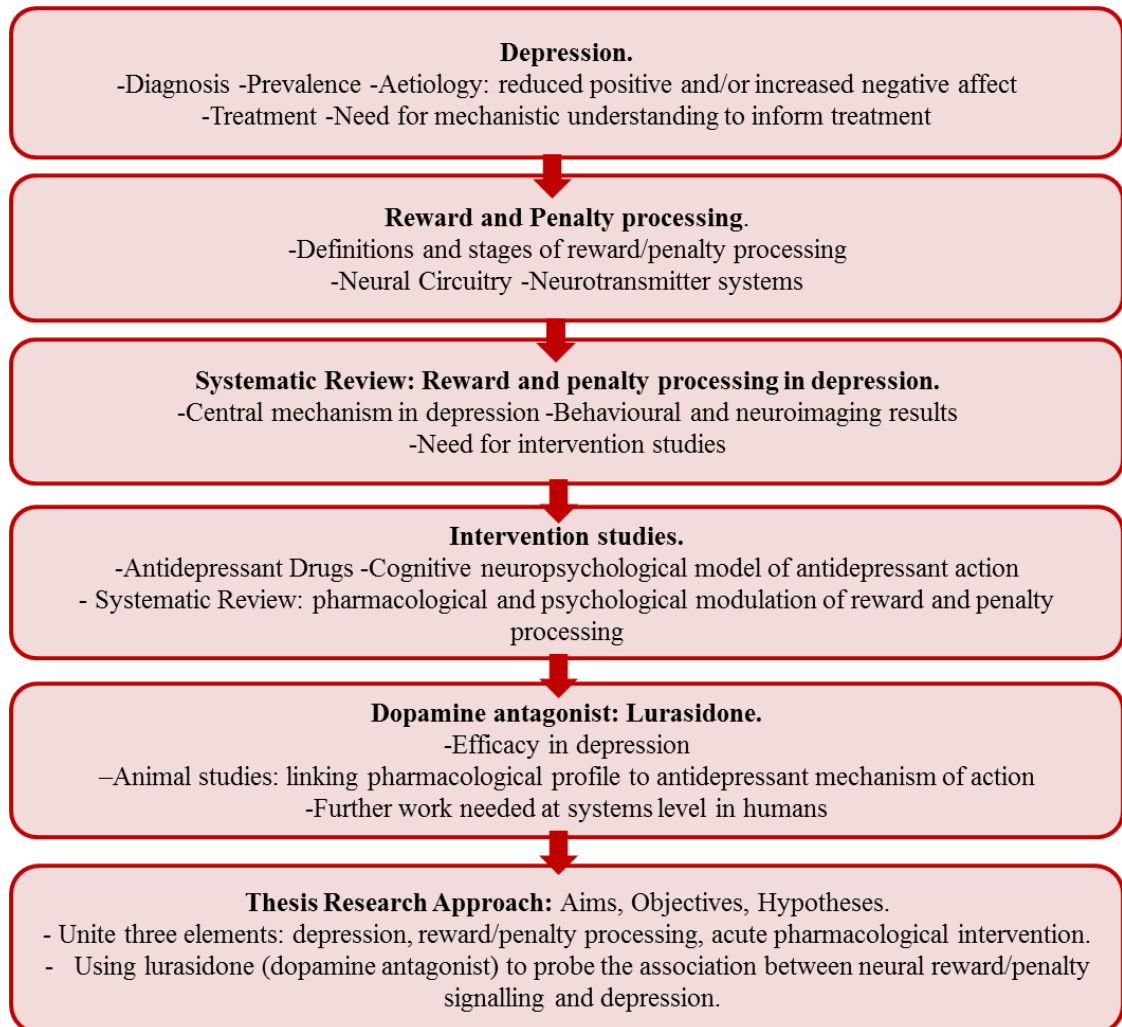


Figure 1.1. Map of Introduction Chapter.

Ultimately, the aim of the introduction is to summarise and integrate three elements: *depression*, the neural underpinnings of *reward/penalty processing* and *acute pharmacological interventions*. This leads to the final section of the introduction in which I present the thesis aims, objectives and hypotheses (using lurasidone (dopamine antagonist) to probe the association between neural reward/penalty signalling and depression).

1.1 Introduction to depression

The first section of the chapter introduces unipolar and bipolar depression and provides a brief overview of the current evidence regarding prevalence, aetiology and treatment options. I then discuss susceptibility and onset of depression within the framework of dual valence systems (Forbes and Dahl, 2005), in which depression is characterised by reduced positive and/or increased negative affect. I discuss the challenges of treating depression and the need to target putative mechanisms of illness in depression. Thus, I review the potential of neuroimaging methods to investigate the neural substrates/mechanisms underlying depressed mood and for relating the dimensional characterisation of depressive symptoms to dysfunction of specific brain circuits.

1.1.1 Clinical presentation and diagnostic criteria

Depression is a common, recurrent, and disabling mental illness. A depressive episode can occur in the context of both unipolar major depressive disorder (MDD) and bipolar disorder (BP).

The diagnostic criteria for depression is summarised in Table 1.1. There are two cardinal symptoms: low mood and anhedonia (according to DSM IV and DSM-5) (Stringaris et al., 2013). A diagnosis requires that an individual displays at least one of these cardinal symptoms alongside other symptoms such as sleep and appetite disturbances, and psychomotor agitation or retardation.

The current major diagnostic manuals, the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5; American Psychiatric Association, 2013) and the 10th Revision of the International Classification of Diseases (ICD-10; World Health Organization, 1992) show essentially the same diagnostic features for a ‘major depressive episode’ (DSM-5) or ‘depressive episode’ (ICD-10) (i.e. a clinically significant severity of depression). This is shown in Table 1.2. However, these manuals differ in the thresholds as the DSM-5 requires a minimum of 5 symptoms, whilst the ICD-10 requires four. Thus, the DSM-5 identifies higher severity cases. Moreover, the DSM-5 recognises the importance of considering the duration of depressive symptoms independently of severity or number of symptoms. Therefore, it

has developed a new category ‘persistent depressive disorder’ which requires a two year duration and fewer number of symptoms.

Table 1.1. DSM-5 criteria for a major depressive episode. Taken from Cleare et al., (2015) with permission.

Major Depressive Episode:	
A Over the last 2 weeks, five of the following features should be present most of the day, or nearly every day (must include 1 or 2):	
1. depressed mood	
2. loss of interest or pleasure in almost all activities	
3. significant weight loss or gain (more than 5% change in 1 month) or an increase or decrease in appetite nearly every day	
4. insomnia or hypersomnia	
5. psychomotor agitation or retardation (observable by others)	
6. fatigue or loss of energy	
7. feelings of worthlessness or excessive or inappropriate guilt (not merely self-reproach about being sick)	
8. diminished ability to think or concentrate, or indecisiveness (either by subjective account or observation of others)	
9. recurrent thoughts of death (not just fear of dying), or suicidal ideation, or a suicide attempt, or a specific plan for committing suicide.	
B The symptoms cause clinically significant distress or impairment in functioning.	
C The symptoms are not due to a medical/organic factor or illness.	
Episodes are classified as mild (few symptoms beyond minimum, mild functional impairment), moderate (minimum symptoms and functional impairment between mild and severe), severe (most symptoms present, marked or greater functional impairment).	
Persistent Depressive Disorder:	
Depressed mood for most of the day, for more days than not, for 2 years or longer.	
Presence of 2 or more of the following for the same period:	
1. Poor appetite or overeating	
2. Insomnia or hypersomnia	
3. Low energy or fatigue	
4. Low self-esteem	
5. Impaired concentration or indecisiveness	
6. Hopelessness	
Never without symptoms for 2 months.	

^aadapted from American Psychiatric Association (2013).

Table 1.2. Classification of depressive states according to the DSM-5 and ICD-10. Taken from Cleare et al., (2015) with permission.

Classification used in Guideline	DSM-5 ^a (code)	ICD-10 ^b (code)
Major depression	Major depressive episode, single episode or recurrent (296)	Depressive episode, severe (F32.2), moderate (F32.1) or mild with at least 5 symptoms ^c (F32.0) Recurrent depressive disorder current episode severe (F33.2), moderate (F33.1) or mild with at least 5 symptoms ^c (F33.0)
Subthreshold depression (includes ‘minor’ depression)	Depressive disorder not otherwise specified (311)	Depressive episode, mild with 4 symptoms ^c (F32.0) Recurrent depressive disorder current episode mild with 4 symptoms ^c (F33.0)
	Adjustment disorder with depressed mood/ mixed anxiety and depressed mood (309)	Mixed anxiety and depressive disorder (F41.2) Adjustment disorder – depressive reaction/mixed anxiety and depressive reaction (F43.2)
	Persistent Depressive Disorder (300.4)	Other mood [affective] disorders (F38) Dysthymia (F34.1)

a. 5th Revision of the American Psychiatric Association’s Diagnostic and Statistics Manual (American Psychiatric Association, 2013).

b. 10th Revision of the International Classification of Diseases (Bauer et al., 2007).

c. For list of symptoms see Table 3. Must include at least two of (i) depressed mood, (ii) loss of interest or pleasure, (iii) decreased energy or increased fatigability.

The inherent heterogeneity of depression may conceal distinct causal processes and pathways in the development of depression. Yet, it is of clinical importance to characterise these different symptom profiles and their respective severity. For

example, anhedonia (reflecting reduced interest, activity and enjoyment), strongly predicts poor antidepressant outcome (Uher et al., 2008). This finding was robustly replicated in STAR*D data (Uher et al., 2012). Moreover, in the Treatment of Resistant Depression in Adolescents (TORDIA) trial, anhedonia was the only dimension (of the 5 dimensions of the Child Depression Rating Scale (CDRS)) to predict a longer time to remission, and fewer depression-free days with a selective serotonin reuptake inhibitor (SSRI) (McMakin et al., 2012). Thus, anhedonia profiles may call for a different treatment approach as compared to individuals presenting with low mood (Uher et al., 2012). A further discussion of dimensional approaches is in Section 1.1.4.

1.1.2 Depression: importance. (Descriptive Epidemiology: the size and nature of the problem)

Depression is a major public health problem, ranked among the top ten leading causes of disability and morbidity worldwide (Collins et al., 2011). Depression is associated with significant physical, emotional, and behavioural problems in social, family, and employment contexts (Maughan et al., 2012) in addition to suicide-related risk behaviours (Sharp et al., 2012). As shown in Figure 1.2, depression reaches its peak incidence in adolescence and young adulthood, and after onset, depression typically runs a life-time course (Birmaher et al., 2007; Thapar et al., 2012; Phillips et al., 2013; Perlis et al., 2009). Depression has a cumulative prevalence of 10% by age 16 (Costello et al., 2003) and adolescents with major depression are up to 30 times more likely to die of suicide (Brent et al., 1992). A meta-analysis showed that one-year and lifetime prevalence of MDD was 4.1% and 6.7% respectively, with females having 1.5-2.5 times higher prevalence than males. This meta-analysis pooled rates from 23 studies, and it should be noted that it gave prevalence rates about half the rates that are commonly reported (e.g. Kessler et al., 2003). This could be due to problems of recall bias when assessing lifetime risk, and prospective studies have shown that lifetime risk could be up to 40% in females (Andrews et al., 2005). In addition to profound personal suffering, MDD places a staggering economic burden on society with an estimated annual cost of \$210.5 billion (Greenberg et al., 2015; Kleinman et al., 2003) in the USA. In summary, depression is a global public health concern, has its origins in early life, and is potentially lethal.

Adolescents may be particularly prone to MDD because of the physical and socio-affective maturation processes that occur during this period (Davey et al., 2008; Greimel, 2011). These maturation processes include dramatic biological changes within the brain, affecting the neural bases of reinforcement processing (Rubia, 2013). Specifically, the most robust evidence for the relationship between depression risk and reduced striatal response to reward has been found during mid-adolescence; a time in development when healthy low-risk groups show maximal striatal response to reward (compared to both childhood and adulthood, Figure 1.2) (Luking et al., 2016c). This may best be explained by adolescence being a time of maximal difference between the subcortical (e.g. nucleus accumbens) structures that mature earlier and the cortical (PFC) structures that only reach full maturity in early adulthood (age 26) (Casey and Jones, 2010). Thus, the developmental imbalance between cortical and subcortical systems may provide new insights into the mechanisms mediating depression in adolescents and young adults.

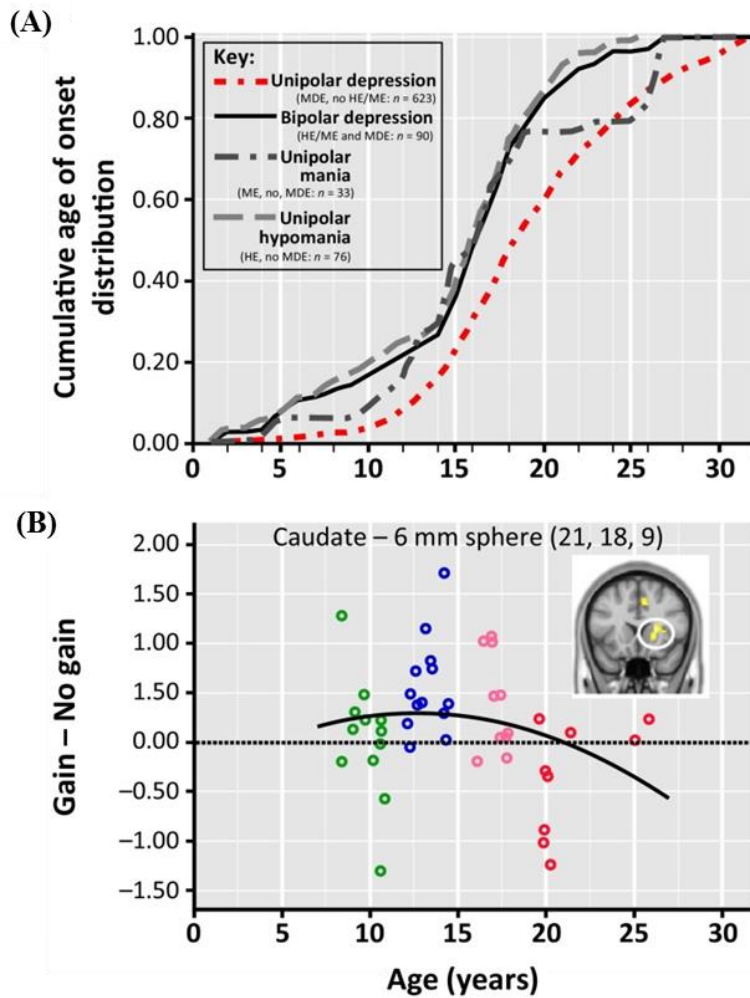


Figure 1.2. (A) The onset of major depressive episodes (MDEs) begins to sharply increase around age 12–15. Red dotted line illustrates the cumulative age of onset for individuals with unipolar depression (i.e. with MDE, without manic episodes, ME). HE: hypomania (adapted from Luking et al., (2016) and Beesdo et al., 2009). (B) Striatal response to monetary reward shows a quadratic (i.e. inverted U shape) relationship with age from childhood to adulthood. Mid-adolescence (12–15years) shows peak striatal response (adapted from Luking et al., (2016) and Van Leijenhorst et al., (2010)).

1.1.3 Aetiology

1.1.3.1 *Depression as a disorder of reward and penalty processing (hyporesponsivity to reward and hypersensitivity to penalties and punishment)*

Early studies used field study experiments and demonstrated that depression is associated with (i) low rates of response-contingent positive reinforcement (ii) high rates of punishing events and (iii) low reward value of positive events and high aversiveness of negative events.

In these field study experiments, participants monitored the daily occurrence of pleasant activities and depressed mood. These studies showed an association between number of pleasant activities experienced daily and depressed mood in depressed, non-depressed psychiatric controls and healthy volunteers (Grosscup and Lewinsohn, 1980; Lewinsohn and Graf, 1973; Lewinsohn and Libet, 1972). Moreover, depressed individuals reported less engagement in pleasant activities compared to non-depressed psychiatric controls and healthy controls (Lewinsohn and Graf, 1973; Macphillamy and Lewinsohn, 1974). Similar to research on pleasant events, a relationship was found between self-reported daily fluctuations in depressed mood and aversive events both in depressed patients (Grosscup and Lewinsohn, 1980) and college students (Rehm, 1978). This finding is considered to be relatively robust given the different measures of mood and unpleasant events reported across studies. Moreover, studies contrasting diagnostic groups demonstrated that the frequency of unpleasant events differentiated depressed and non-depressed controls, even after controlling for the frequency of pleasant events (Lewinsohn et al., 1985). Further studies also demonstrated elevations on total unpleasant events in depressed versus healthy control groups (Lewinsohn and Talkington, 1979).

An elaboration on these behavioural models included the proposition that depression originates not only from inadequate engagement in pleasurable activities and excessive experience of aversive events (i.e. frequency), but also characterised by diminished reward value of pleasant events and increased aversiveness of unpleasant events (i.e. subjective ratings). Indeed, daily ratings found reduced subjective enjoyability of events in depressed individuals (Macphillamy and Lewinsohn, 1974) and that

depressed participants rated unpleasant events as more aversive than healthy controls (Lewinsohn and Talkington, 1979).

More contemporary research that integrates neuroscience and laboratory paradigms for studying the effects of reward and punishment in depression supports the evidence from the field studies described above. These studies are examined in extensive detail in the literature review in Section 1.5. In particular, Figure 1.12 in Section 1.5 illustrates how clinical terminology and phenomena map onto the science of reward processing. For now, it is sufficient to mention that evidence converges with the notion that depressed individuals exhibit deficits in motivation, reward learning and responsiveness to reward (Henriques and Davidson, 2000; Henriques et al., 1994; Treadway et al., 2012) and heightened sensitivity to negative events and avoidance (Elliott et al., 1997a; Elliott et al., 1996; Eshel and Roiser, 2010; Lewinsohn et al., 1973) relative to healthy subjects. These behavioural phenotypes correspond to altered function in a circumscribed network of brain regions, particularly fronto-striatal-limbic systems which are innervated by dopamine and are associated with approach-related behaviour (Pizzagalli et al., 2005). Of note, the cardinal symptom of anhedonia has received increasing attention in the study of reward in depression. The impaired ability of depressed individuals to modulate behaviour as a function of reinforcement, reduced motivation to expend effort, and reduced activity in the ventral striatum during reward anticipation is largest in patients reporting anhedonic symptoms and has been found to be uniquely associated with anhedonia rather than general distress (Pizzagalli et al., 2008; Stringaris et al., 2015; Treadway et al., 2012). As such, this thesis is devoted to probing the neural circuits, including the striatum, anterior cingulate cortex, orbital frontal cortex, insula (etc.), that are part of a reward system and are implicated in depression and anhedonia (Section 1.3).

The observational and experimental evidence have been converged into a theoretical framework. Figure 1.3 illustrates Lewinsohn's behavioural model for the causes, correlates, consequences and maintaining processes in depression. Here, an individual with low rates of response-contingent positive reinforcement and/or elevated rate of aversive experiences may develop depressed mood via mechanisms such as increased focus on one-self, self-criticism, and negative expectancies. Subject to persistent dysphoric emotions and thoughts such individuals may exhibit a decreased motivation to seek and a reduced ability to experience reward (Drevets, 2001). Moreover,

depressed individuals may be sensitive to the saliency of punishing stimuli, and they may act to minimise exposure to such negative outcomes. Punishment avoidance could be adaptive in some circumstances. However, the continual use of a strategy to avoid negative outcomes in a rigid or context-insensitive manner is likely to reduce the probability of being exposed to rewarding environments. This in turn, may exacerbate depressive symptoms (Smoski et al., 2008). Thus, avoiding risk often will lead to missed opportunities for rewards. In light of this, engaging in an increasing number of rewarding experiences, and a decrease in the experienced aversiveness of events is associated with clinical improvement in depression (Grosscup and Lewinsohn, 1980; Richards et al., 2016). Indeed, Behavioural Activation (BA) (described in Section 1.1.5.1), as part of cognitive-behavioural therapy requires depressed patients to increase behaviours that lead to a sense of self-efficacy and mastery, as well as those that result in pleasurable consequences (Jacobson et al., 1996). However, in BA individuals pursue some form of reward while exposing themselves to potential punishment. For example, engaging in social activities carries the possibility of positive (e.g. making friends, having fun) and negative consequences (e.g. social exclusion, criticism). Thus, it involves a dual process of increasing approach-related behaviours and reducing sensitivity to punishment avoidance strategies, both of which are important factors in the maintenance of depression (Chapman et al., 2007; Martin-Soelch, 2009). It is also important to note that this model links to a learned helplessness model in which catastrophic responses to perceived failure (which are correlated with depression severity (Elliott et al., 1997a; Elliott et al., 1996)) could bias future actions and cause a cycle of learned helplessness (Klein et al., 1976; Seligman, 1972).

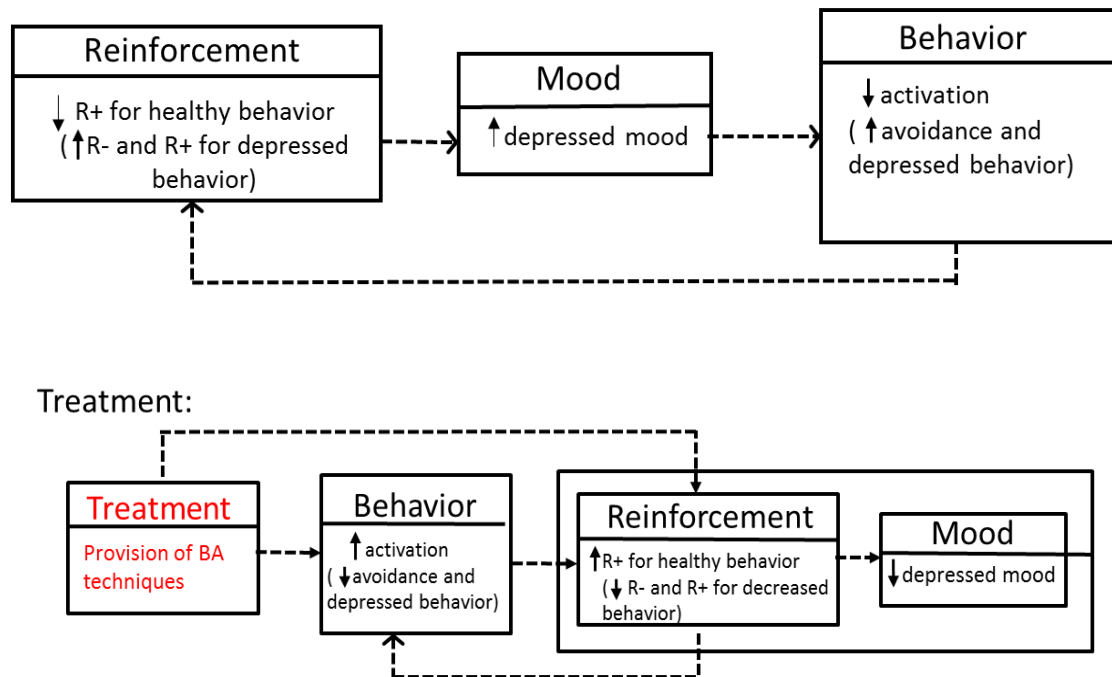


Figure 1.3. Schematic illustration of Lewinsohn's behavioural model of depression. Causes, correlates, consequences and maintaining processes in depression involve low rates of response-contingent positive reinforcement and/or elevated rate of aversive experiences, leading to increased depression (via increased focus on one-self, self-criticism, negative expectancies), leading to reduced engagement and increased avoidance of activities/interpersonal, thereby perpetuating the cycle. Treatment-induced increases in positive reinforcement and reduced sensitivity to punishment avoidance lead to reductions in depression.

1.1.4 Categorical and dimensional approaches to researching depression

One of the major issues for clinicians and guidelines is that categories help to guide decision-making, however, illnesses seem to exist along a continua (Cleare et al., 2015; Matthews and Hampshire, 2016; Plomin et al., 2009; Rose and Barker, 1978) (Figure 1.4). There is now a greater emphasis on thinking of depression along a continuum of severity from normal sadness to severe impairment and illness (Angst et al., 2000; Ayuso-Mateos et al., 2010; Lewinsohn et al., 2000; Paykel and Priest, 1992). Researching quantitatively also involves harnessing the potential of unselected population-based cohort studies in youth, and studying dimensions across all individuals. Indeed, surveys in communities have shown that key symptoms of depression are common in the community and exist across the whole range of severity

(Jenkins et al., 1997). This research approach is in line with the Research Domain Criteria (RDoC) framework (Morris and Cuthbert, 2012) (e.g. as in (Stringaris et al., 2015b) where symptom levels are related to the brain measurements). It also does justice to findings concerning the genetic underpinnings of common mental illness (Plomin et al., 2009) as well as current approaches to understanding neural system perturbation in a dimensional way (Matthews and Hampshire, 2016). Thus, these research strategies (which are consistent with the overarching aims of the RDoC (Insel et al., 2010)) - may provide greater sensitivity for detecting aetiological pathways in the depression phenotypes that are otherwise concealed in analyses that take the existing psychiatric classification as the starting point (i.e. group difference analysis).

Increasingly more neuroimaging studies are using a dimensional approach (Holroyd and Umemoto, 2016; Morris and Cuthbert, 2012; Pan et al., 2017; Phillips, 2013; Stringaris et al., 2015a; Whitton et al., 2015). For example, Satterthwaite and colleagues uncovered a common brain mechanism that spans categories of MDD and bipolar depression. They mapped continuous depression severity and anhedonia symptoms to intra-functional connectivity between brain regions implicated in reward processing (Satterthwaite et al., 2014). Stringaris et al., (2015) showed that alterations in the brain's reward network operate as a mechanism across the spectrum of risk for depression (healthy-subthreshold-MDD) in a community sample of adolescents. Thus, for the aforementioned reasons, the current thesis also used a dimensional analytical approach. Please also refer to Methods Section 3.1.1 for a justification of the dimensional recruitment strategy in this thesis.

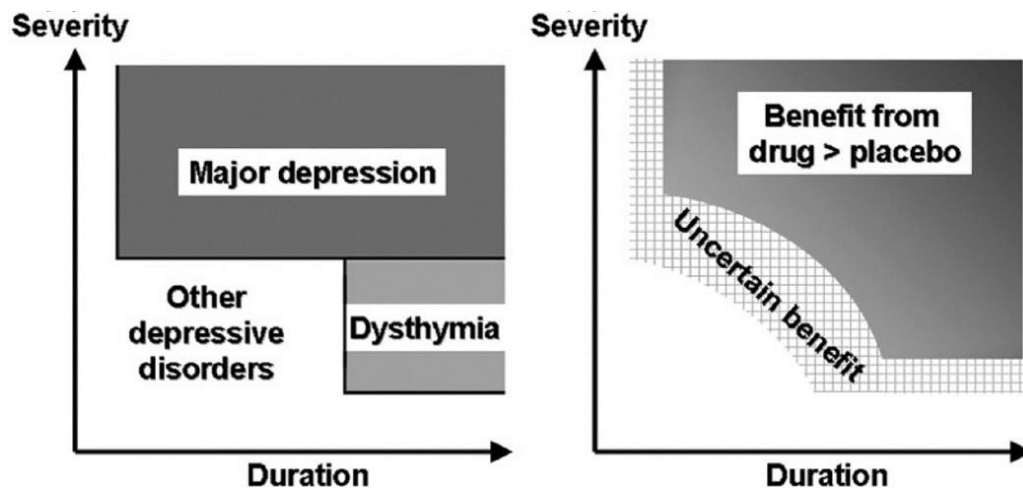


Figure 1.4. A dimensional perspective to depressive disorders and response to treatment. Taken from Cleare et al., (2015) with permission.

1.1.5 Treatment options for depression

1.1.5.1 *Depression: psychological treatment options*

There are a variety of cognitive-behavioural, psychodynamic and systemic psychological approaches available for treating depression. As the systematic review in Section 1.6.3.8 examines how cognitive-behavioural therapy and behavioural activation impact upon reward and penalty processes, I briefly give an overview of these therapies below.

In brief, CBT is a therapy that is time-limited, structured, and focused on the present and specific problem. It is based on the principle that negative thought and belief patterns affect mood and behaviours. Treatment generally involves psychoeducation; strategies to reduce negative beliefs (cognitive restructuring); behavioural procedures (e.g. exposure to fears, behavioural activation); self-esteem enhancement; problem solving; emotion-regulation; acute crisis management; and relapse prevention.

Behavioural activation is a type of cognitive behavioural therapy in which the main focus is on directly changing behaviours by increasing the opportunities for obtaining positive reinforcements from the environment (Jacobson et al., 2001). Expecting a reward or a loss is an important psychological mechanism of BA. The goal of BA is to facilitate patients in expanding access to positive reinforcing activities and in-turn increase the rate of response-contingent positive reinforcement available to them

(Figure 1.3) (Jacobson et al., 2001). In order to achieve this, in BA, patients review activities that make them (or used to make them) feel rewarding and give a feeling of accomplishment and complete behavioural experiments. As a result, patients gradually cultivate reasonable expectations about positively reinforcing activities. BA has received increasing attention as its rationale may be simpler than CBT in general, as it does not require as extensive skills on the part of the therapist or the patient (Ekers et al., 2011a; Ekers et al., 2011b; Hopko et al., 2003). A recent multi-centre, two-arm Phase III, non-inferiority¹ randomised control trial demonstrated that BA is as effective as CBT in terms of depression treatment response measured by the Patient Health Questionnaire (PHQ-9) at 6, 12 and 18 months and less costly to deliver (Richards et al., 2016).

1.1.5.2 ***Depression: pharmacological treatment options***

The prevailing hypothesis of depression over the last decades has been the monoamine hypothesis. This implicates reduced monoamine function in depression (Dale et al., 2015) and hypothesises that acute monoamine potentiation (i.e. increasing the synaptic concentration of monoamines, such as serotonin) is the central mechanism of antidepressant action (Ross and Renyi, 1969). Selective serotonin reuptake inhibitors (SSRIs) (e.g. fluoxetine) and serotonin and norepinephrine reuptake inhibitors (SNRIs) emerged from this research and are currently first-line treatment options for MDD. Tricyclic antidepressants (TCAs) such as amitriptyline seem to be particularly effective in treating melancholic depression profiles, however, they induce anticholinergic and membrane stabilising (quinidine-like) effects which make them poorly tolerated and dangerous in overdose (Cleare et al., 2015). Other selective monoamine reuptake inhibitors, such as the norepinephrine reuptake inhibitor (NRI) reboxetine are available. However, meta-analyses show that it may be less efficacious to SSRIs (Cipriani et al., 2018; Cipriani et al., 2009), and this could be related to its poor tolerability (Wiles et al., 2014) or high placebo response rates (Cipriani et al., 2018). Bupropion is one of the few antidepressants that prevent the reuptake of

¹ As this was a non-inferiority RCT, the investigators aimed to establish whether the clinical effectiveness of BA is *not substantially inferior* to CBT. Unlike usual RCTs where null hypothesis is *no* difference, here the null hypothesis is that there *is* a difference.

dopamine (in addition to noradrenaline) (i.e. dopamine and noradrenaline reuptake inhibitor, DNRI) (Dwoskin et al., 2006; Stahl et al., 2004). It has been suggested that agents that effect dopamine may be more suited to treat apathy and anhedonia (Argyropoulos and Nutt, 2013; Nutt et al., 2007).

Clinical guidelines for the pharmacological treatment of MDD, not only include SSRIs, SNRIs, NRIs and DNRI, but also augmentation or combination treatment with atypical antipsychotics (dopamine/serotonergic antagonism) when an individual does not respond to first-line treatment. First line augmentation treatments include quetiapine and aripiprazole, and second line treatments include risperidone and olanzapine. In contrast to MDD, bipolar depression is not treated with SSRIs as they confer increased mania risk (Connolly and Thase, 2011). Instead bipolar depression is treated with atypical antipsychotics such as quetiapine, olanzapine, risperidone and lurasidone and the mood stabiliser lithium (Loebel et al., 2014c; Suppes et al., 2016b; Tohen et al., 2014).

It is important to note that several other hypotheses of depression have been brought forward in pre-clinical and clinical research and these include blockade of α_2 -adrenoceptors on norepinephrine cell bodies and terminals (e.g. mirtazapine) thereby increasing norepinephrine release, targeting glutamate receptors (e.g. N-methyl-d-aspartate (NMDA) receptor antagonist ketamine) and modulation of cholinergic and γ -aminobutyric acid (GABA)ergic transmission (MacQueen et al., 2017).

1.1.5.3 ***Depression: poorly treated***

Despite the availability of a variety of treatments, up to 40–50% of MDD patients fail to respond to antidepressant medication (Trivedi et al, 2006) or psychological treatment (DeRubeis et al, 2005) and the likelihood of remission (i.e. complete recovery) is even lower (from 30%-45% (Carvalho et al., 2009) to 53%) (Gartlehner et al., 2011; MacQueen et al., 2017). Response to second-line treatment happens only in 50% of non-responders (Brent et al 2008) and about 25% of responders relapse in the next year (Vitiello et al 2011). Moreover, this must be considered in light of recent evidence that RCTs may not only over-estimate efficacy of antidepressants, but also may exaggerate placebo response because of various biases (Wang et al., 2018). It is also striking that despite increases in pharmacotherapy (prescribing medication) (Beck and Patten, 2004), there has not been a reduction in the prevalence of MDD (in

countries which have reported before-after comparisons) (Brugha et al., 2004; Kessler et al., 2005). Thus, depression not responding adequately to treatment is common (Gonzalez et al., 2010) and is responsible for much of the staggering disability and cost associated with depression (Crown et al., 2002; Fekadu et al., 2009; Fostick et al., 2010; Souery et al., 2006).

1.1.6 Depression: poorly understood

Taken together, mechanisms in depression are still poorly understood, and this impacts treatment efficacy. Indeed, there has been little progress in depression genetics (Wray et al., 2018), pathophysiological findings for depression are often inconsistent (Ma, 2013), and there has been a lack of rational drug discoveries. This prompts the need to define other avenues of therapy. Towards this aim, there is a need to understand the various neurobiological mechanisms for depressive symptoms in order to generate specific predictions about treatment development (i.e. “rational treatment advances”) and to detect predictive biomarkers for treatment selection. Recently, reward and penalty related processes have emerged as a promising candidate mechanism, and this is discussed in detail in the ensuing sections.

1.2 **Reward and penalty processing**

As mentioned in the previous section, depression has been conceptualized as an imbalance in dual valence systems (Forbes and Dahl, 2005), involving reduced positive and/or increased negative affect. Core aspects of the disorder may include reduced interest in participating in pleasant activities, reduced opportunities to experience rewarding situations and difficulty activating and sustaining positive emotions (Forbes et al., 2005; Hopko et al., 2003). This may also co-occur with heightened sensitivity to negative outcomes/feedback and biased information processing and representations that mediate choice behaviour, including preferential attention, planning, memory and self-referential processing towards negative information (Beck, 2008; Disner et al., 2011; Gotlib et al., 2010a; Grimm et al., 2009; Sylvester et al., 2003). Some research implicates these processes in the maintenance and onset of depression, and these processes may in turn exacerbate depressive symptoms (Gotlib, 1981; Gotlib and Krasnoperova, 1998; Gotlib et al., 2004; Papageorgiou and Wells, 2003).

Neuroimaging has been valuable in the search for the neural substrates underlying depressed mood, and in Section 1.5, I discuss how neural mechanisms of reward and penalty-related function have recently emerged as a promising candidate. However, before reviewing the behavioural and neuroimaging literature linking aberrations in reward and penalty processing to depression, it is necessary to define some key concepts. In this section, I first define the terms and stages of reward and penalty-related processing, and experimental paradigms which are used to probe these various processes. I then outline the neural circuitry underlying reward and penalty-related processing (from animal and human literature) and an overview of various theories of dopamine function in reward and penalty processing.

1.2.1 **What is reward? What is penalty?**

A rewarding stimulus is one that, through the activation of a distributed and integrated set of neural systems, leads to a hedonic reaction ('liking') and generates motivation to approach the stimulus ('wanting') (Berridge and Kringelbach, 2008; Richards et al.,

2013). In contrast, a punisher or penalty could be either the absence of a reward or an aversive stimulus that leads to an aversive reaction and motivates behaviour away from the stimulus.

1.2.2 **Primary versus secondary rewards**

Rewards and punishers have been categorised into primary and secondary categories. Primary rewards consist of stimuli which have a direct positive value for an individual receiving the reward (i.e. reinforce behaviours without having to be learned). Primary rewards or punishments have a physiological meaning, like pleasant and unpleasant food, beverages, sounds and pain. In contrast, secondary rewards (e.g. money, power, some forms of social acknowledgment), have no immediate direct value, and gain reward value through the learning of stimulus-reward associations. Valuation of primary rewards may depend on the state of the organism (e.g. hunger, thirst), and may be more rewarding under circumstances of deprivation. However, secondary rewards are less prone to saturation and therefore possess a relative stable value.

Stimulus types are important considerations in neuroimaging literature, as demonstrated by a meta-analysis that assessed how representations of primary and secondary rewards overlap in the human brain (Sescousse et al., 2013). They showed that monetary, erotic and food reward engaged a common brain network including the ventromedial prefrontal cortex, ventral striatum, amygdala, anterior insula and thalamus. But there were also key differences, with for example, secondary monetary rewards being presented in evolutionary more recent cortical regions, whilst food and erotic (i.e. primary) rewards being more strongly represented in the insula and amygdala (Figure 1.5). Thus, experienced reward value recruits a core “reward system” as well as reward type-dependent brain structures (Sescousse et al., 2013).

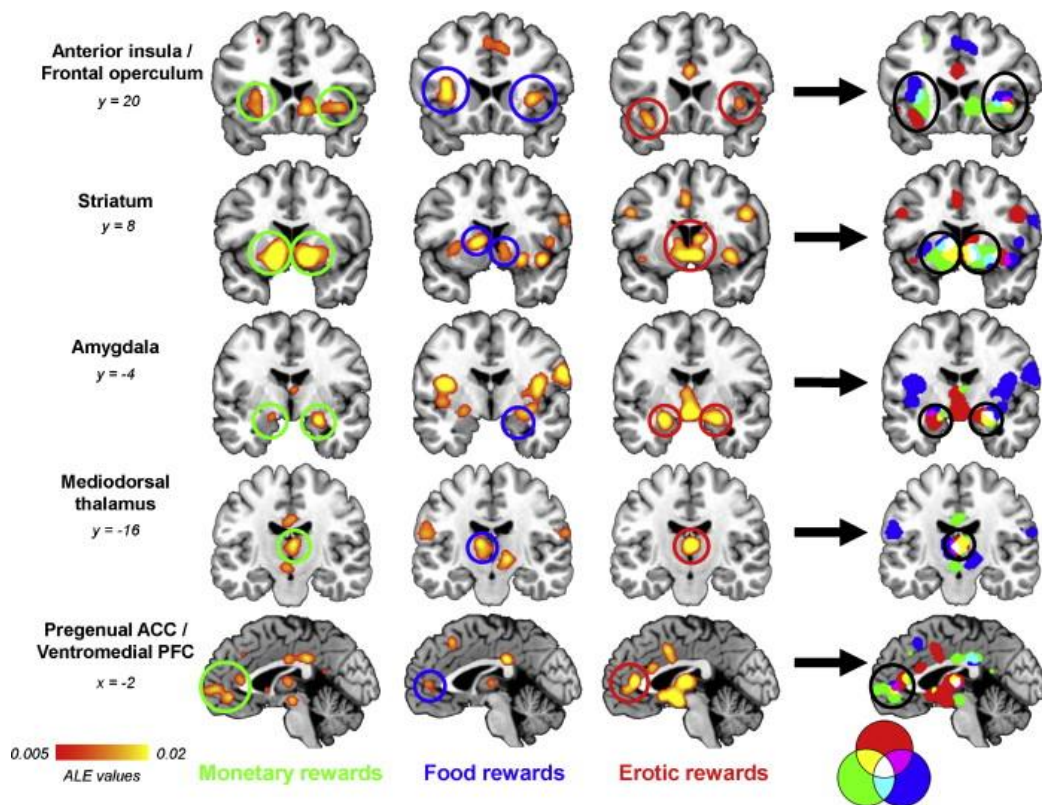


Figure 1.5. Illustration of brain regions consistency and commonly activated by monetary, erotic and food reward outcomes (green = monetary rewards, red = erotic rewards, blue = food rewards). Taken from Sescousee et al., (2013) with permission.

1.2.3 Incentive-based processing

Coupling stimuli and actions with positive (reward) or negative (penalty) outcomes facilitates the selection of appropriate actions so that the organism can change their behaviour to maximise reward and minimise punishment. Thus, adequately encoding reward and penalty-related information and relating it to action is essential for adaptive behaviour and survival (Gottlieb et al., 2014; Hikida et al., 2016), as well as subjective pleasure and well-being (Berridge and Kringelbach, 2015). Many brain regions are involved in different levels of incentive based learning, from those that regulate basic survival functions, to those underlying higher cognitive control for decision making. These are discussed in more detail in Section 1.3. When outcomes deviate from expectations, these links change to control future behaviour and this is discussed in more detail in Section 1.4 (Prediction Error).

Approach behaviours are those that move the organism towards rewards, whilst avoidance behaviours are those that move the organism away from punishers. In addition, rewards and punishers facilitate learning through positive or negative

reinforcement respectively (Bissonette et al., 2014). A reward (or absence of a punisher) following a behaviour will make the future occurrence of that behaviour more likely and this often elicits subjective feelings of pleasure. In contrast, behaviours following punishers (or lack of rewards) will make the future occurrence of that behaviour less likely (Bissonette et al., 2014). Punishment stimuli can consist of the presentation of aversive stimuli or the removal of an appetitive stimulus (often operationalised as monetary loss) in response to certain behaviour (Lutz and Widmer, 2014). As discussed in Section 1.1.3.1, reductions in reports of pleasure and approach-related behaviour, (and vice versa for punishers) are prominent features of depression.

1.2.3.1 *Stages of reward and penalty processing*

Reward and penalty processing can be considered as a composite construct, consisting of multiple components. Each phase reflects a different psychological state and separately shapes human behaviour (Pizzagalli et al., 2009a). Thus, distinguishing between these phases is important for understanding which aspects of reward or penalty processing might be dysfunctional in depression, or how different symptoms of depression are related to precise facets of hedonic function.

In terms of reward processing, this has been described by Rizvi et al., (2016) in seven phases. These are summarised in Figure 1.6. For reward processing the stages can be summarised as follows: (i) building a stimulus-reward association through learning and repeated pairings, leading to (ii) interest/desire (wanting a reward), (iii) anticipation (a state of readiness for a reward), (iv) motivation (initial energy expenditure to attain a reward), (v) effort (sustained energy expenditure to attain a reward), (vi) consummation (i.e. hedonic response to reward), and (vii) feedback integration (updating reward presence and values). Although the reward process has been described as a linear process, it is important to note that on a behavioural level, these aspects of reward can occur simultaneously. For example, an individual can feel interested and anticipating a reward, and the effort that is made to attain a reward can also be pleasurable in its own right.

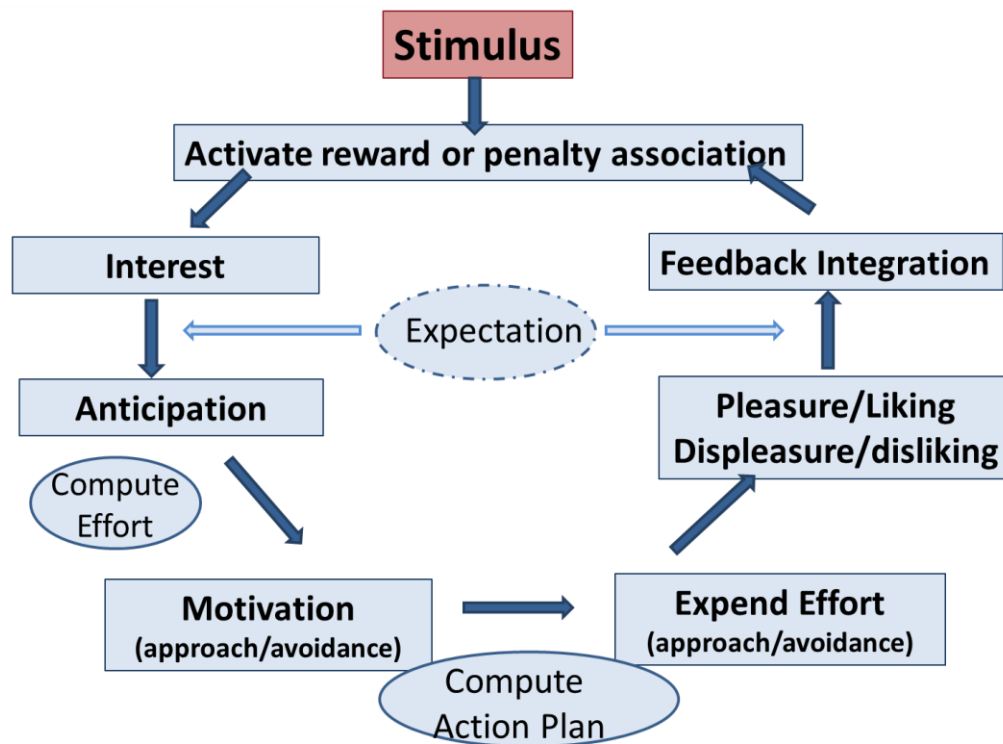


Figure 1.6. Model of the stages of reward and penalty processing, adapted from Rizvi et al., (2016) with permission.

1.2.4 Types of task

There are various types of task that are designed to tap into different phases of reward or penalty processing (see Figure 1.12 in Section 1.5). One of the most extensively used paradigms is the Monetary Incentive Delay (MID) task (Knutson et al., 2000) and has been applied across clinical and non-clinical populations in conjunction with functional neuroimaging. It has been shown to robustly activate a fronto-striatal-limbic network (see meta-analyses: Bartra et al., 2013; Diekhof et al., 2012; Kerestes et al., 2014). Moreover, the MID has good test-re-test reliability. Plichta et al., (2012) showed that the MID task evokes robust activation in the ventral striatum with high effect sizes of VS-mean summary values (ES: 0.96-1.43) and excellent group-level activation reliability at the whole brain level and within target Regions of Interest (ROIs) (intraclass correlation coefficient (ICC): 0.94). Moreover, within-subject reliability of ROI-mean amplitudes across sessions was fair to good for the MID task (ICCs = 0.56-0.62), thereby suggesting that the task is suited for within-subject designs (Plichta et al., 2012; Wu et al., 2014).

A full description is given in Methods Section 3.5, but in brief, the task is an example of an *instrumental reward task* that requires participants to press a button as fast as possible (instrumental action) preceded by an incentive cue and followed by feedback. For example, participants receive a reward (a sum of money) in a reward trial or avoid losing in a penalty trial if they respond to the target within an individually titrated response window. Variations in the task include introducing different reward valences, i.e. the positive states associated with reward receipt (or absence of a penalty) vs. negative states associated with loss (or reward omission).

This thesis used an adaptation of the original MID task from Knutson et al. (2001), to include three trial types where participants gain (reward trial), lose (penalty trial) or do not win/lose (no-incentive trial). In this way, the MID task allows for the investigation of all four types of outcome in the consummatory phase (reward (successful response), missed reward (missed response), penalty (missed response), and avoided penalty (successful response)). In this study positive outcomes were operationalised as monetary gains, and negative outcomes or penalties were operationalised as loss by deducting a certain amount of money from the participant's credit. This is because missed rewards and losses are qualitatively distinct processes (with different expectation-outcome contingencies) and are likely to elicit varying degrees of aversive responses (Knutson et al., 2001). This same framework can be used to understand the differences between two kinds of positive outcomes: rewards and avoided losses.

There are other *reward decision-making tasks*, which tend to be similar to the instrumental-reward tasks such as the MID, with the only difference that the participants are given the opportunity to choose between two or more instrumental actions. An example of such task would be the Effort-Expenditure for Rewards Task (EEfRT) (Treadway et al., 2009b) or wheel of fortune task, which has been used to explore the effort-based decision-making associated with anhedonia.

Last of all, some studies have utilised *passive tasks*, which involves passive viewing or tasting of appetitive (happy, pleasant e.g. chocolate), aversive (unpleasant e.g. moldy strawberries), and neutral stimuli (Guyer et al., 2007; McCabe et al., 2010).

1.3 **The neural circuitry of reward processing**

The concept of an anatomically identifiable ‘reward circuit’ originates from animal studies showing that electrical stimulation in specific mid-brain sites is highly reinforcing. Indeed, early studies with intra-cranial self-stimulation to the medial forebrain bundle demonstrated that rats would maintain rapid rates of more than 2,000 responses per hour for a continuous period of 26 hours, ignore available food and would only slow on the basis of physical exhaustion (Olds, 1958; Routtenberg and Lindy, 1965). Several brain regions form part of this incentive-based learning circuit, however, on the basis of self-stimulation, pharmacological, physiological, and behavioural studies, the nucleus accumbens (NAcc) and ventral tegmental area (VTA) dopamine (DA) neurons appear to be at the centre (Haber and Knutson, 2010; Hikosaka et al., 2008; Rolls, 2000; Wise, 2002). The cell bodies of midbrain DA neurons lie in the densely packed dorsal sector of the substantia nigra (pars compacta) and the more medially located VTA. The principal targets of ascending DA projections include other subcortical structures (principally the striatum), various limbic structures (e.g. amygdala and insula) and parts of the frontal cortex (e.g. orbital frontal cortices (OFC), anterior cingulate cortices (ACC)). These are illustrated in Figure 1.7.

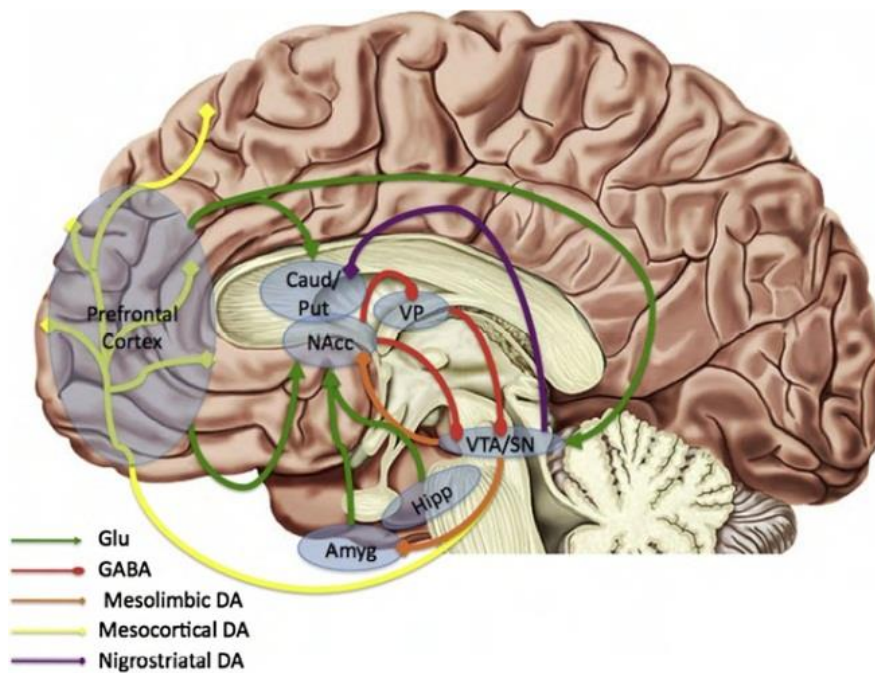


Figure 1.7. A schematic illustration of mesolimbic, mesocortical and nigrostriatal pathways. The diagram shows DA nuclei within the ventral tegmental area projecting to the nucleus accumbens and prefrontal cortex, and within the substantia nigra projecting to the dorsal striatum (caudate and putamen). Inhibitory firing from the ventral pallidum maintains DA firing rates at tonic levels. Excitatory projections from prefrontal cortex project, amygdala and hippocampus synapse on striatal targets, including the NAcc. The NAcc sends GABAergic projections to the ventral pallidum, suppressing inhibition of VTA, thereby facilitating phasic burst firing of VTA DA neurons. Figure taken from Treadway and Zald, (2011) with permission.

There is now a wealth of evidence from studies of functional neuroimaging (fMRI and PET) in unselected samples of human subjects, that link reward and penalty processes to this dopamine-rich fronto-striatal-limbic neural circuit (Boschen et al., 2011; Delgado et al., 2008; Eshel and Roiser, 2010; Jensen et al., 2007; Pohlack et al., 2012; Quevedo et al., 2017). Meta-analytic evidence suggests that specific neuroanatomical areas of the network underlie various facets of reward and penalty processing, including desire, anticipation of reward, effort to attain rewards or avoid penalties, consummation and cognitive aspects of learning stimulus-outcome associations (Bartra et al., 2013; Diekhof et al., 2012; Haber and Behrens, 2014). Below, I provide an overview of the intrinsic organisation and anatomical projections of the main regions of the circuit (striatum, amygdala, insula, OFC and ACC), and how this relates to its particular functions.

1.3.1 The striatum

Organisation of the striatum: The striatal dopamine neurons appear to be at the centre of the reward network (Haber and Knutson, 2010). The striatum is a large subcortical structure and has a high density of DA receptors, which is the common target of all antipsychotic medications. Anatomically, the striatum can be divided into three main sections. The putamen and the caudate are separated by the internal capsule and together form the dorsal striatum, whilst the ventral striatum (VS) is formed of the ventral caudate (head), ventral putamen and nucleus accumbens (NAcc) (Haber and McFarland, 1999; O'Doherty et al., 2004).

Connections of the striatum: The striatum is a heavily interconnected structure. The NAcc, caudate and putamen receive connections from the Ventral tegmental area (VTA) and substantia nigra via the mesolimbic and nigrostriatal DA projections respectively (Oades and Halliday, 1987), as well as from the ventral pallidum, and thalamus. An important distinction between the dorsal and VS, is that the VS alone receives a dense projection from the limbic areas: amygdala and hippocampus (Friedman et al., 2002; Fudge et al., 2002; Haber and Knutson, 2010). Cortico-striatal terminal projections from the prefrontal cortex (PFC) are organised in a function topographic manner in the striatum. Specifically, the ventromedial PFC (vmPFC), orbital frontal cortex (OFC) and anterior cingulate cortex (ACC) project primarily to the rostral striatum, with the vmPFC projection most medially (to the NAcc), the ACC most laterally, and the OFC terminal ending between these two portions. However, it is also important to note increasing evidence that projections for the vmPFC, OFC and ACC also converge in sub regions of the VS, thereby suggesting functional integration or an anatomical substrate for modulation between these circuits. Efferent projections from the striatum project primarily to the midbrain and the pallidum (Haber et al., 1990; Parent et al., 1997). A schematic illustration of the connections and associated neurotransmitters of the ventral striatum are shown in Figure 1.8 and Figure 1.9.

To summarise, the convergence of mid-brain, limbic and prefrontal projections to and from the striatum, places the striatum as a key entry port for processing emotional and motivational information that in turn drives action output. The specific functions of the striatum, both from animal and human literature are described briefly below (see Haber and Behrens, (2014) for an extensive review).

Functions of the striatum: The ventral striatum has most strongly been associated with stimulus-reward and stimulus-penalty learning. Once it is learned that a given stimulus will be followed by a reward or punishment, VS activation occurs to increasingly distal reward and punishment-predictive cues (Cromwell and Schultz, 2003; Wassum et al., 2012). Indeed, ventral striatal dopamine firing and BOLD response seems to encode prediction error (PE). PEs reflect the deviation of actual outcomes from their expectations and this is covered in detail in Section 1.4. PEs guide outcome prediction to gain future rewards and to avoid potential losses (Boksem et al., 2008; Montague et al., 2004). Specifically, the VS displays a response pattern in which activation increases when anticipating rewards, but decreases when the anticipated reward is not obtained (Knutson et al., 2003). The VS response is greatest when rewards or punishments occur unpredictably (Cohen et al., 2005; Yacubian et al., 2006; Yacubian et al., 2007). This implies that the role of the VS during reward consummation may be best understood in terms of tracking the PE (McClure et al., 2003; O'Doherty et al., 2003). Specifically, dopamine release in the VS is necessary for reward learning that attributes incentive salience or 'motivational wanting' to reward cues (Berridge, 2007; Berridge and Kringelbach, 2015; Berridge et al., 2009; Flagel et al., 2011). In the context of punishments, dopamine release is related to motivated action away from a punisher (McCullough and Salamone, 1992; Salamone and Correa, 2012; Salamone et al., 1994; Tidey and Miczek, 1996; Young, 2004). Dopamine-based brain manipulations in rodents powerfully and specifically change incentive salience without altering hedonic reactivity (Cagniard et al., 2005). VS activation is higher, the larger the rewards, suggesting that the region is involved in coding expected reward magnitude (Yakubian et al., 2007). The body and tail of the caudate and putamen (i.e. dorsal striatum) seem to be most involved in the translation of incentives into goal-directed actions that promise higher amounts of reward in the future (i.e. stimulus-response-reward learning) (Delgado et al., 2007; Alexander and Crutcher, 1990; Haruno and Kawato, 2006). Effortful responses to obtain a reward are correlated with signal change in the caudate and putamen and inactivation of the caudate abolishes such actions (Aharon et al., 2001; Diciano and Everitt, 2004). Moreover, striatal activation may shift from more dorsal to ventral activation with age (Kerestes et al., 2014).

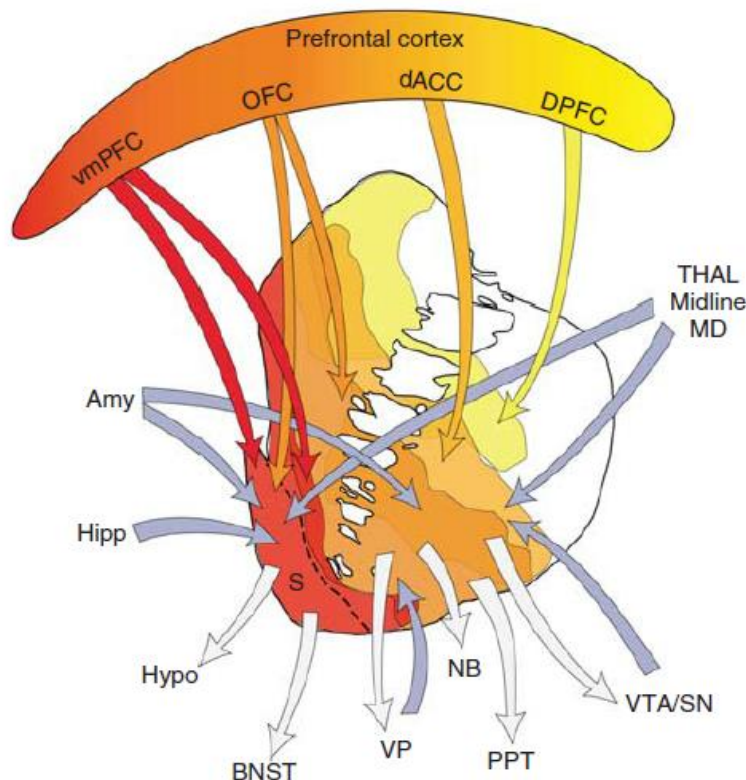


Figure 1.8. Schematic illustrating the connections of the ventral portion of the striatum. Taken from Haber and Knutson, (2010) with permission. Blue arrows = inputs; Grey arrows=outputs; Amy=amygdala; BNST=bed nucleus stria terminalis; Dacc=dorsal anterior cingulate cortex; Hipp=hippocampus; Hypo=hypothalamus; MD=medio-dorsal nucleus of the thalamus; OFC=orbital frontal cortex; PPT=pedunculopontine nucleus; S=shell; SN=substantia nigra, pars compacta; STN=subthalamic nucleus; Thal=thalamus; VP=ventral pallidum; VS= ventral striatum; VTA=ventral tegmental area; vmPFC=ventral medial prefrontal cortex.

1.3.2 Insula

The insula and the anterior portion of insula in particular have been primarily linked to the processing of aversive information (Liu et al., 2011; McCabe et al., 2012; Sescousse et al., 2013; Waechter et al., 2009). A meta-analysis directly compared reward valences and revealed that whilst the NAcc and OFC were more active in response to positive versus negative rewards, the anterior insular cortex was involved in the processing of negative reward information (Liu et al., 2011). This observation ties in with a medial-lateral distinction for positive versus negative rewards (Kringelbach, 2005; Kringelbach and Rolls, 2004).

The insula appears to be critical for the interface between cognitive and affective processing. For example, the insula is activated during both aversive pavlovian conditioning (e.g. anticipation of punishers) and aversive trace conditioning (Buchel et al., 1999; Buchel et al., 1998; Chua et al., 1999). Moreover, insula activity is modulated by perceptual awareness of threat (Critchley et al., 2002), penalty (Elliott et al., 2000), or error-related processes (Menon et al., 2001). Insula activation also seems to be involved in pain intensity coding (Ploghaus et al., 2001; Tracey et al., 2000; Davis, 2000). A study by Paulus et al., (2003) demonstrated that insular activity was greater when individuals selected a risky versus a safe response and when the probability of selecting a safe response followed a punished response. Moreover, this response was correlated with measures of harm avoidance. These results suggest that insula activation represents aversive somatic markers that guide risk-taking decision-making behaviour (Paulus et al., 2003). This is in line with the insula's anatomical connections, receiving input from dorsolateral prefrontal and posterior parietal cortex (Selemon and Goldman-Rakic, 1988) and the amygdala (McDonald et al., 1999). Moreover, in healthy control samples, model-based fMRI has illustrated that penalty-related PEs are more strongly associated with insular BOLD activity than reward-related PEs (Garrison et al., 2013). Thus, signalling punishment prediction error following outcome might be the computational mechanism by which the insula facilitates negative value learning. Whilst making decisions, the insula might signal cue negative value (i.e. punishment prediction), which could drive avoidance behaviour. Indeed, damage to the anterior insula specifically impairs punishment avoidance (Palminteri et al., 2012). To summarise, the insula is predominantly involved in evaluative roles of negative responses, and as negative affect is usually associated with risk, that insula is involved in anticipation of risky decision, especially for uncertainty—averse responses in anticipation of loss.

1.3.3 Amygdala

As described in Section 1.3.1, the amygdala has direct connections with the VS and the VTA. The amygdala is a prominent limbic structure. It provides contextual information which is used for adjusting motivational level to upcoming rewards and

punishers. Indeed, the ACC and amygdala estimate costs and benefits of potential options. The amygdala appears to be particularly important in the context of penalties (Zald, 2003) or when rewarding stimuli are devalued (Baxter and Murray, 2002; Gottfried et al., 2003). However, when controlling for arousal, direct comparison of amygdala responses to rewards versus penalties tends to show no significant differences. This implies that amygdala activation in fMRI may respond more to stimulus arousal rather than valence/value (Anderson et al., 2003; Small et al., 2003). Last of all, the amygdala has shown to be sensitive to DA modulation during reward processing in healthy volunteers (Murray, 2007a; O'Daly et al., 2014; Russo and Nestler, 2013; Tye et al., 2010a).

1.3.4 **Orbital frontal Cortex (OFC)**

Several cortical regions have been implicated in top-down, regulatory functions during reward and penalty-related processing. The orbitofrontal cortex (OFC) is another region whose involvement in reward processing has been extensively documented in animal studies. The OFC receives somatosensory, visual and olfactory inputs, and as such, has been shown to take part in representing the reward value of primary reinforcers such as touch, smell and taste (Rolls, 2000, 2016). Single-cell recording of neurons in the PFC have shown that they respond to the taste of glucose and that the neuronal response reduces when the monkey has been fed to satiety with the same taste (Rolls, 1989). In contrast, neurons in the primary taste cortex show sustained responses and are not modulated by satiety, thereby suggesting that OFC neurons encode reward value rather than detection of taste. Moreover, OFC lesions seem to abolish behavioural flexible responses, which lead to perseveration errors on reward reversal tasks (Clarke et al., 2008; Izquierdo et al., 2004). This demonstrates the OFC's role in updating stimulus-reward associations on the basis of changes in reward contingencies. Thus, the OFC represents incentive, rather than sensory features of stimuli and have been associated with effort-related decision making that guide behaviour (Walton et al., 2003). In human fMRI studies, this region tends to respond to contextual aspects of reward during anticipation, such as the anticipated magnitude and probability of rewards, and to a lesser degree to penalty-related cues (Knutson et al., 2005; Yacubian et al., 2006).

1.3.5 Anterior Cingulate Cortex (ACC)

The ACC involves the integration of diverse striatal and prefrontal functions and this is reflected by its anatomical position with many pathways leading through the ACC (Haber and Knutson, 2010). These functions involve comparing valued options during reward anticipation and choosing among them to channel choice into a motor response. The ACC and VS show functional connectivity at rest (Pan et al., 2017) and input from the ACC to the VS allows for flexible deployment and adaptation of behaviour to changing circumstances (Alexander and Brown, 2011; Holroyd and Coles, 2002b; Holroyd and Umemoto, 2016; Holroyd and Yeung, 2012; Shahnazian and Holroyd, 2017; Umemoto and Holroyd, 2016; Walsh and Anderson, 2012; Walton et al., 2007). Electrophysiological (EEG) studies have shown that the Feedback Negativity (FRN), an event-related potential which indicates the early appraisal of feedback and appears larger following the presentation of negative feedback, has its origins in the ACC (Gehring and Willoughby, 2002; Hajcak et al., 2005; Holroyd and Coles, 2002b; Holroyd et al., 2004; Yeung et al., 2005). Specifically, an FRN signal may be generated as ACC neurons shift from encoding expected to actual outcomes (i.e. a Prediction Error signal) (Hyman et al., 2017). The ACC is an interesting example as it seems to encode both reward and penalty-related types of prediction errors, as shown in primate (Amiez et al., 2006) and human studies (Holroyd and Coles, 2002; Nieuwenhuis et al., 2005; Oliveira et al., 2007). This could be related to different sub-regions, with pre-genual ACC being related solely to reward prediction errors whereas antero-medial ACC activity correlated with both reward and penalty prediction errors. The antero-medial ACC has been associated with conflict-monitoring (Botvinick et al., 2004) or error detection (Carter et al., 1998), and this could explain why the ACC encodes both reward and penalty-related PEs.

To summarise, I have outlined the circuitry that underlies the intertwined and highly connected networks that provide the substrate for functional integration of incentive-based learning. To develop an adaptive behavioural response to rewards and penalties, information about motivation and the stimuli need to be combined with a strategy and an action for obtaining goals. The dopamine-rich striatum is at the centre of the network receiving and providing inputs to midbrain, limbic (amygdala and insula) and cortical (OFC, ACC) structures. In the cortex, orbital networks link stimuli with

outcomes; connections to ventral medial regions provide motivational input; cingulate regions integrate such value signals with action representations. The insula and amygdala seem to be primarily involved in the processing of negative reward information, using aversive somatic markers that guide risk-taking decision-making behaviour. Now that I have outlined the major dopaminergic pathways; in the next section, I go into further depth about the hypothesised roles of the key neurotransmitter, dopamine, in reward and aversion.

1.4 Reward and Dopamine

1.4.1 Dopamine's role in reward: hedonia, prediction error, incentive salience

The first theory for dopamine's role in reward suggested that brain dopamine systems mediate unconditioned pleasure or 'liking' responses which are produced by primary (food, sex) reinforcers as well as the conditioned pleasure from secondary reinforcers (Wise, 2008). Indeed, this founded the '*hedonia hypothesis*'. However, later studies used intelligent behavioural paradigms to show that dopamine is not necessary or sufficient for generating hedonic 'liking' responses (Berridge, 2007; Berridge et al., 2009; Berridge et al., 1989). Since these early studies it now seems that dopamine has a more specific role in incentive salience, reward learning and other processes, which I will now discuss in turn.

Incentive salience was termed by Berridge and colleagues and refers to the 'wanting', 'motivating' or 'desire' attribute of a rewarding stimulus (Berridge et al., 2009). Thus, when incentive salience is attributed to a reward-related stimulus it transforms a mere perception or memory into a motivationally potent incentive that commands attention and induces approach behaviours. Incentive salience has been mapped to the NAcc (Berridge and Kringelbach, 2015). A central premise to this theory is that reward processing is a composite construct, consisting of multiple components such as reward-related learning, 'wanting' to obtain a reward and the 'liking' or pleasure experience when one interacts with the reward (Berridge, 2007; Berridge et al., 2009). Berridge and colleagues have argued that dopamine causes 'wanting' for rewards, more than 'liking' or learning for those rewards (see Figure 1.9).

For example, increases in extracellular dopamine in mice (produced by genetic manipulation or microinjections of amphetamine to the NAcc) failed to increase hedonic 'liking' reactions to sucrose rewards (Cagniard et al. 2005; Pecina et al. 2003; Wyvell and Berridge 2000). Moreover, hyperdopaminergic mouse, with 170% higher levels of extracellular striatal dopamine, showed higher behavioral 'wanting' for sucrose on several instrumental, approach, and consumption measures. However, the mice did not show better or faster instrumental learning, Pavlovian learning, and learned stimulus-response patterns were not stronger than normal (Cagniard et al.

2005; Yin et al. 2006). The hyperdopaminergic mouse also failed to show higher 'liking' reactions to sucrose taste, despite its higher 'wanting' for these rewards (Peciña et al. 2003). This model suggests that elevated dopamine is a sufficient cause for elevated 'wanting' (but not for elevated 'liking' or learning). A study by Flagel et al., (2011) bred 'sign-tracker rats' that had much higher release of dopamine in the NAcc in response to a conditioned stimulus than an unconditioned stimulus and 'goal-tracking rats' that did not show a differential response to the CS and US. Importantly, the CS evoked dopamine release in both sign- and goal-tracking rats, but this signal increased to a greater degree in sign-trackers, as they attributed incentive salience to the CS. Dopamine blockade abolished the sign-tracking conditioned response, but kept a goal-tracking CR intact (Flagel et al., 2011). Again, this suggests that dopamine is an integral part of stimulus–reward learning that is specifically associated with the attribution of incentive salience to reward cues. It seems that opioid, endocannabinoid and GABA neurotransmitter systems are more closely tied to consumatory phases of reward processing, as demonstrated in rodents sweet tasting (Berridge et al., 2009).

Another important piece of evidence against the hedonia hypothesis is that striatal mechanisms in general and NAcc dopamine in particular participate in aspects of aversive learning, responsiveness to aversive stimuli and punishment (e.g. shock, tail pinch, restraint stress, aversive conditioned stimuli, aversive drugs, social defeat) (McCullough and Salamone, 1992; Salamone and Correa, 2012; Salamone et al., 1994; Tidey and Miczek, 1996; Young, 2004). Indeed neuroimaging has shown the association between human NAcc activity and response to aversive processes and motivation to avoid negative outcomes (Liu et al., 2011). Thus, there is an emphasis on mesolimbic and nigrostriatal DA in reinforcement learning and motivational behaviour (Salamone and Correa, 2012; Yin et al., 2008). There is still uncertainty as to whether there are distinct DA neurons that respond differentially to appetitive and aversive stimuli, and what proportion of neurons respond to each. Nevertheless, it is clear that phasic DA activity can be enhanced by at least some aversive conditions, and therefore is not specifically tied to positive reinforcement (Figure 1.9).

PHASES OF MOTIVATED BEHAVIOR:
(e.g. “seeking” vs. “taking”)

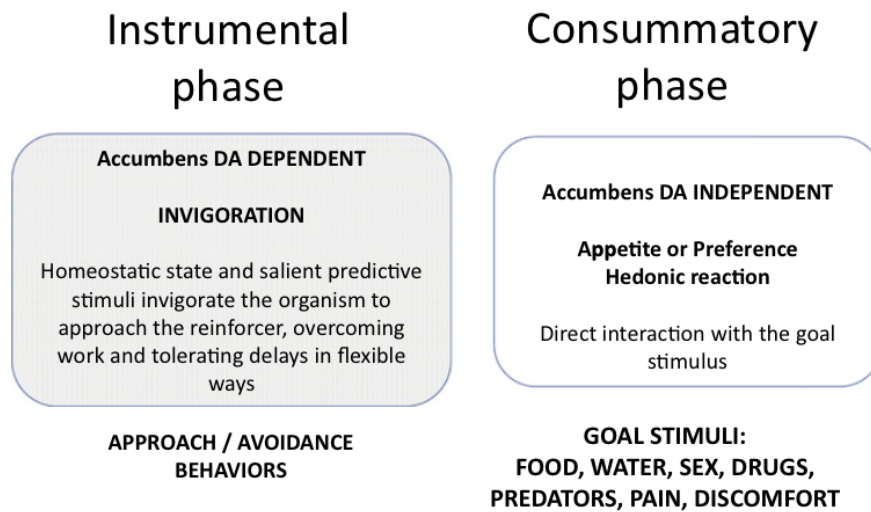


Figure 1.9. Nucleus Accumbens dopamine in motivated behaviour (approach for rewards, avoidance for aversive stimuli), and lack of involvement in the consummatory phase of subjective liking and aversion responses. Taken from Salamone and Correa (2012) with permission.

In contrast to the incentive salience hypothesis, it has been argued that dopamine signalling encodes the distinction between a predicted reward and a received reward, and thus encodes a *prediction error (PE) teaching signal*. Schultz and colleagues formulated the prediction error hypothesis on the basis of single-cell recording experiments from midbrain dopaminergic neurons in the substantia nigra and VTA of awake monkeys whilst they engaged in an instrumental or pavlovian conditioning task (Ljungberg et al., 1992; Schultz, 1998; Schultz and Romo, 1990). In a typical experiment, a thirsty monkey was seated before two levers. After a visual stimulus was presented on screen, the monkey had to press one of two levers to receive a juice reward (Figure 1.10). During the early phase of learning, dopamine neurons displayed a phasic burst in activity only at reward delivery. However, after several trials, the monkey learnt the correct stimulus-action-reward association and dopaminergic neurons no longer fired to the reward. Instead, there was a temporal shift of dopamine firing to the presentation of the cue, alongside anticipatory licking behaviour. If an expected juice reward was omitted, the neurons responded with a dip of activity below basal firing rate at the time at which the reward would have been received. This has been termed as a *negative PE* (when the outcome is worse than expected). There is a

positive PE when the outcome is better than expected (i.e. delivery of unexpected rewards), eliciting a phasic activation, and a reward that occurs exactly as predicted in value and time elicits no phasic change in dopamine neurons (*null prediction error*). This suggested that dopaminergic activity is sensitive to both the occurrence and timing of the reward, and coded for a prediction error signal described as the difference between the reward and its prediction (Figure 1.10 and Figure 1.11, Model 1) (Schultz, 2016). This positive and negative PE signal has been consistently produced in both humans (Garrison et al., 2013) and animals (Cohen et al., 2012) using a variety of tasks and neuroimaging modalities (Schultz, 2016). In particular, positive dopamine prediction error activation promotes behaviour that leads to increased reward, whilst negative dopamine prediction error ‘dips’ do not.

It is also important to mention that although rewards and reward predicting stimuli have objective, physical properties, the utility of the reward is determined by the needs of the individual and is therefore intrinsically subjective. Numerous studies have now shown that the value of outcomes reduces (or are ‘discounted’) by delays in reward delivery. This is referred to as ‘temporal discounting’ and describes the preference of sooner, but smaller rewards over larger later rewards. Neurons in several brain regions, including the dorsal and ventral striatum, OFC and PFC show this property of temporal discounting. Thus, a modification of the original PE models of reward learning proposes that dopamine neurons encode subjective value as opposed to objective value in temporal discounting. In this way the neurons are key inputs into value-based decision making processes. As such, the dopamine PE signal uses teaching signals of the Rescorla-Wagner (Kremer, 1978) and temporal difference (TD) (Morita et al., 2012; Sutton, 1988) RL models.

The Rescorla–Wagner (RW) model (see Figure 1.10 for equation) is a formal model of instrumental and Pavlovian conditioning and describes the associative strength between a conditioned stimulus (CS) and an unconditioned stimulus (UCS). Change in associative strength between a CS and an UCS is a function of differences between what was predicted (i.e. the animal’s expectation of the UCS, given all the conditioned stimuli present on the trial) and what actually happened in a conditioning trial. In other words, we make predictions about what will happen and we compare these predictions to what actually happens. If the prediction is wrong, then the difference between what was predicted and what actually happened is used for learning. The idea that

prediction error signals can take on both positive and negative response characteristics is the central feature of this form of learning model.

Whilst the RW model is trial based and estimates predicted reward pertaining to a particular stimulus across trials, the TD model estimates the future-predicted reward from discrete time-points i within a trial until the end of the trial (Schultz et al., 1997). Indeed, timing of different stimuli within learning trials influences how associative strength changes and is a critical factor in modulating the efficacy of conditioning (Sutton, 1988). In this way, the TD model also overcomes some of the initial limitations of the RW model such as an inability to learn sequential stimulus-based predictions (e.g. when one stimulus predicts another stimulus which in turn predicts reward). For example, once it is learned that a given stimulus will be followed by a reward, phasic dopamine release in the NAcc occurs to increasingly distal reward-predictive cues (Cromwell and Schultz, 2003; Wassum et al., 2012).

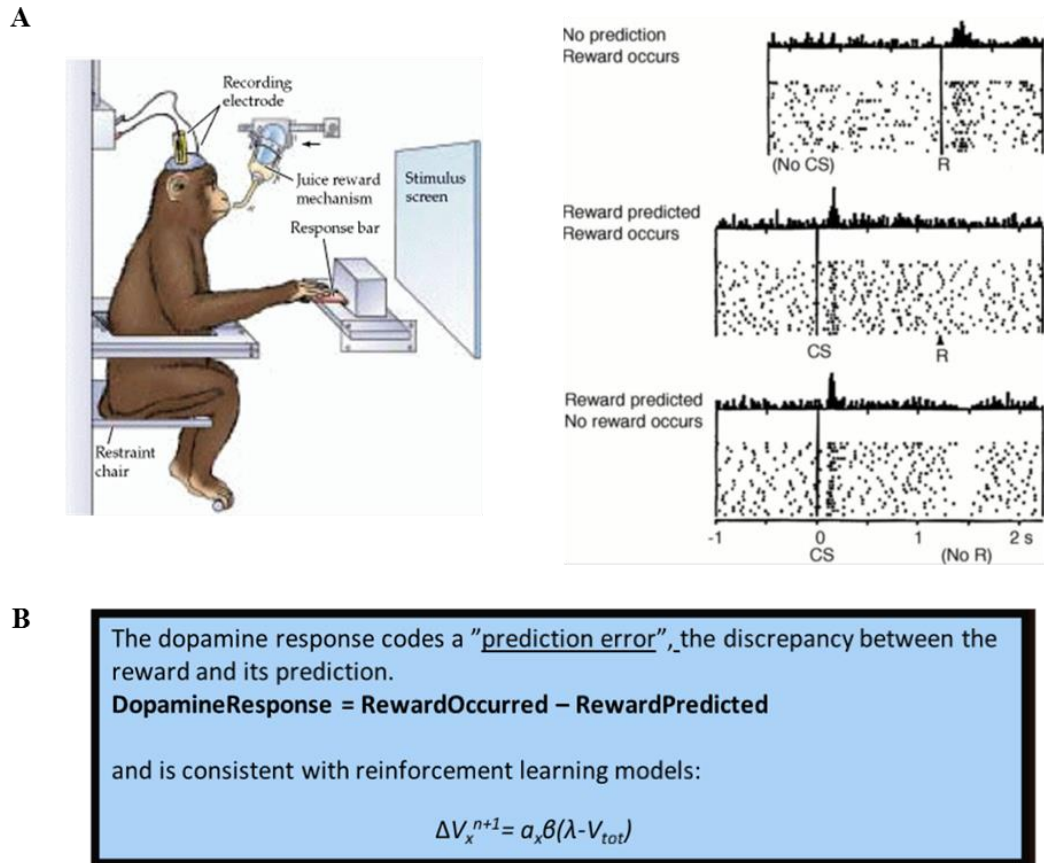


Figure 1.10. Prediction Error Hypothesis (A) Peri-event time histogram demonstrating the firing rate of a dopaminergic neuron in a monkey's midbrain. Adapted from Schultz et al., (1997). (Top panel) Prior to learning, a drop of appetitive fruit juice occurs in the absence of a conditioning stimulus and the unpredicted nature of the stimulus activates the neuron. (Middle panel) After learning a cue is associated with the reward and predicts its occurrence (stimulus-action-reward contingency), the dopamine neuron responds to the cue but fails to be activated by the predicted reward itself. (Bottom panel) After learning, the conditional cue elicits a response, but the reward fails to occur due to the monkey not making the required behavioural response. The activity of the dopamine neuron is depressed exactly at the time when the reward would have occurred. Original sequence of trials is plotted from top to bottom. CS: conditioned, reward-predicting stimulus; R: primary reward. (B) Rescorla-Wagner learning model where: ΔV_X is the change in the strength, on a single trial, of the association between the Conditioned Stimulus labelled "X" and the Unconditioned Stimulus. α is the salience of X (bounded by 0 and 1). β is the rate parameter for the US (bounded by 0 and 1), or 'association value'. λ is the maximum conditioning possible for the US. V_X is the current associative strength of X. V_{tot} is the total associative strength of all stimuli present (X plus others).

1.4.2 **Integration of perspectives**

The roles of dopamine in prediction error (reward learning) and incentive salience have thus far been considered as separate, competing hypotheses. However, recent studies (Hamid et al., 2016; Syed et al., 2016) which recorded the dynamics of NAcc dopamine concentrations during an instrumental learning task suggest that these theories can be integrated and considered within one framework. Specifically, they demonstrated that phasic dopamine bursting contributed to learning and incentive salience simultaneously. Reward is anticipated by an increase in phasic dopamine firing which encodes the predicted reward value (before the stimuli appears) and only under circumstances when an overt action is required. This implies that initial phasic dopamine activity encodes expected value, which promotes reward seeking through action/movement (Collins and Frank, 2016; Hamid et al., 2016; Syed et al., 2016). Indeed, an experiment in humans, which controlled for reward learning histories, showed that individuals had learned preferences for actions which they had freely chosen relative to actions that were not chosen (Hamid et al., 2016). (Figure 1.11 (Martins et al., 2017) shows how trial-to-trial presentation of reward-predicting cues, when an action is required, elicits progressive ramping-up in DA encoding expected value. If a reward occurs or is omitted then there is a sudden jump or dip in value, mimicking a reward or penalty prediction error respectively. Whilst the expected value ‘ramps up’, there is decline in PE signal due to learning (on a trial-by-trial basis) and the presence of a fixed phasic dopamine peak. In support of this model, Hamid et al., (2016) showed that if dopamine phasic activity is manipulated before choice, it impacts the incentive or willingness to work for a reward without affecting learning. In contrast, if dopamine phasic activity is altered during actual reward impacts upon learning. Thus, although there is a role of dopamine release in learning, it is strongly associated with coding for the value of a motivation to promote action (Collins and Frank, 2016). This view brings together both phasic and tonic dopamine levels rather than viewing these as separate roles.

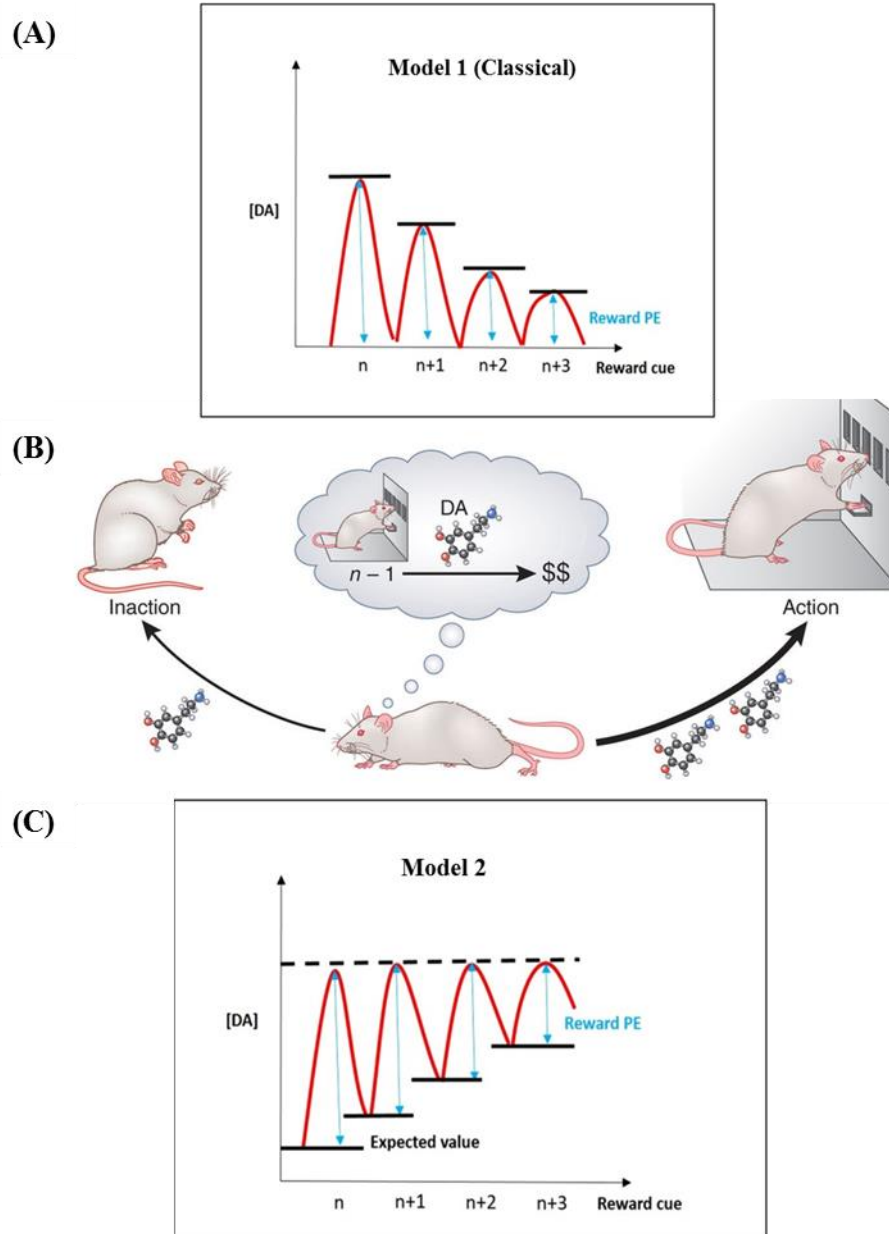


Figure 1.11. Functions of dopamine (DA) in action and learning. (A) Model 1: Phasic dopamine transients encode prediction error (PE) signals. The phasic DA peak and PE decreases with learning, reflecting an increase in the predictability of reward value and timing, in the presence of a fixed *baseline* of DA. (B) DA concentration signals the value of overt action and directly incentivises choice accordingly. DA signals a reward prediction error during reward on trial $n - 1$, thereby reinforcing the value of the action so that it is incentivising on trial n . (C) Model 2: Phasic dopamine transients encode reward value (expected and actual). A reward cue elicits a phasic jump and ramping up in DA-encoding expected value, when an overt action is required. Reward occurrence or omission leads to a sudden jump or dip in value, mimicking a reward or penalty prediction error. Whilst the expected value ‘ramps up’, there is decline in PE signal due to learning (on a trial-by-trial basis) and the presence of a fixed phasic dopamine *peak*. Adapted and taken from Collins and Frank, (2016) and Martins et al., (2017) with permission.

1.4.3 **What is the relationship between reward BOLD signal and dopamine?**

We have therefore seen that a host of methods including optogenetics, microdialysis, voltammetry and single-cell recording have been used in animals to formulate hypotheses for dopamine's role in incentive-based learning and action. However, the method used in this study is in-vivo non-invasive neuroimaging using Blood-Oxygen-Level-Dependent Magnetic Resonance Imaging in humans. Thus, an important assumption and question is whether BOLD signalling is related to dopaminergic activity. Indeed, there is evidence that an increase in DA release is spatially and temporally correlated to an increase in BOLD signal in the context of reward processing (Knutson and Gibbs, 2007; Schott et al., 2008b). Recently, a direct link has been found between reduced mid-brain transporter density and neural activity during reward processing within the mesolimbic pathway in healthy and depressed human participants (Dubol et al., 2017b). Nevertheless, ascribing the changes in BOLD signal to one or more receptor systems is highly speculative as the precise mechanism by which BOLD signal is modulated cannot be determined with fMRI alone.

Moreover, several studies have used computational models to demonstrate that BOLD signal in various brain regions links to Prediction Error. Functional MRI studies of prediction error are generally based on a Rescorla-Wagner or Temporal Difference modelled prediction error. These are implemented in various learning algorithms (e.g. SARSA, Q-Learning, advantage learning) such that the estimated PE is calculated for each stimulus event. The time series described is subsequently regressed onto the acquired fMRI images to determine voxels in which the estimated PE correlates with the BOLD activation value (O'Doherty et al., 2004; O'Doherty, 2004). This highlights one of the advantages of the PE model, namely its testability.

These studies have shown that PEs are encoded in the prefrontal cortex (PFC) including the ACC, VS and other midbrain structures such as the ventral tegmental area (VTA). PE-signals have also been detected in the insula and amygdala (Gradin et al., 2011; Seymour et al., 2004). However, valence (e.g. reward versus punishment, monetary gain versus loss) is controversial and there are suggestions that there are both overlapping and distinct brain regions encoding reward- and penalty-related PEs. For example, a meta-analysis in healthy volunteers showed that activity in the striatum

and prefrontal cortex correlates with reward PEs, whereas punishment PEs are reflected by insular activity (Garrison et al., 2013). Another meta-analysis found a high degree of overlap in the brain regions encoding both expected or experienced wins and losses (Liu et al., 2011).

At a mechanistic level of explanation, Kumar et al., (2008) have suggested that phasic DA neuronal firing leads to DA release which could facilitate longer duration postsynaptic activity, such as post-synaptic potentiation and inhibition (Kumar et al., 2008; Menon et al., 2007b). They propose that these longer post-synaptic responses could underlie the BOLD signal that correlates with the predicted TD signal (Menon et al., 2007a). This could also account for both the activations and deactivations described by the predicted TD signal.

1.4.4 **Interim summary**

In summary, this section has summarised stages of reward and penalty processing, behavioural tasks that probe these processes as well as brain and neurotransmitter systems that underlie reward and penalty processing. Several brain regions form part of an incentive-based learning circuit including meso-cortical, meso-limbic and nigrostriatal pathways, for which the neurotransmitter, dopamine is of key importance. Although commonly referred to as the ‘brain’s reward circuit’, this circuit equally responds to aversive stimuli. Dopaminergic neurons are involved in numerous processes including motivation and reward- and aversion-related cognition (mesolimbic pathway), as well as executive processes including inhibitory control, cognitive flexibility, attentional control (mesocortical pathway). Dopamine’s precise contribution to learning (via prediction error), ‘wanting’ (incentive salience) or ‘liking’ has been the source of much debate. Recent evidence suggests that incentive salience and prediction error models can be integrated within the same framework, with DA release in learning coding for the value of a motivation to promote an action.

We thus have an emerging picture in which depression has been conceptualised as an imbalance in dual valence systems (reduced positive and/or increased negative affect. (Forbes and Dahl, 2005), and I have outlined brain and neurotransmitter systems which underlie processing of rewards and penalties. In the next section I bring these

two components together by directly examining behavioural and neural deficits of reward- and penalty-related processing in depression.

1.5 **Systematic Review: Reward and penalty-related processing in Depression across electrophysiological and fMRI studies.**

This chapter will examine reward- and penalty-related processing as a central mechanism in depression. I provide a systematic review of behavioural and neuroimaging evidence of aberrations in reward and penalty processing in depression. Specifically, I focus on case-control studies, familial depression risk studies, longitudinal studies and intervention studies. Prior to this, it is important to conceptually bridge clinical terminology with the science of reward processing.

For the purpose of mapping reward processing events to experimental equivalents and their clinical phenomena in depression, the several phases of reward processing (described in Figure 1.6, Section 1.2.3.1) can be parsed into four sets of reward processing events: *prediction decision*, *action* and *experience*, Figure 1.12 below).

The *prediction* stage involves activating existing knowledge about the value of the object. Anticipatory anhedonia, defined as a lack of interest in activities that used to be enjoyable (Treadway and Zald, 2011), is the clinical, depressive symptom that is most related to this phase. In translational terms, the prediction stage tends to be the reward or penalty anticipation phase of the experiment when a cue indicates to the subject whether a win or loss is to be expected. A typical task that is used to examine this is the Monetary Incentive Delay (MID) task (Knutson et al., 2001), although there are others too (e.g. Wheel of Fortune Task, Card Guessing Task).

The second *decision* stage involves computing the cost associated with attaining a reward. Depressed individuals commonly show difficulties in volition or motivation (Kendler, 2016; Kendler, 2017) which best map onto this phase of processing. Translationally, this stage links to the decision stage of the experiment (e.g. of a gambling task) whereby the individual chooses between available options.

The third *action* stage is where motor effort is required in order to approach a reward or to avoid a punisher. Complaints such as low energy and fatigue are commonly reported by depressed individuals, and are most related to this phase (Kendler, 2016; Kendler, 2017). Translationally, the action phase involves the individual making an

action, such as button press or lever presses, and this provides a measurable way to examine task-related effort responses (e.g. the Effort Expenditure for Rewards Task) (Treadway et al., 2012; Treadway et al., 2009a).

The forth *experience* phase encompasses the consummation of reward and the subjective feelings that are associated with it (e.g. enjoyment). It also involves feedback integration, so that future rewards can be assessed on the basis of past experience. Consummatory anhedonia, defined as the lack of pleasure in activities or experiences that used to be pleasant (Treadway and Zald, 2011), best maps onto this stage. In translational terms, this corresponds to the phase in which an individual is presented with the outcome (e.g. win outcome, loss outcome) in the MID task.

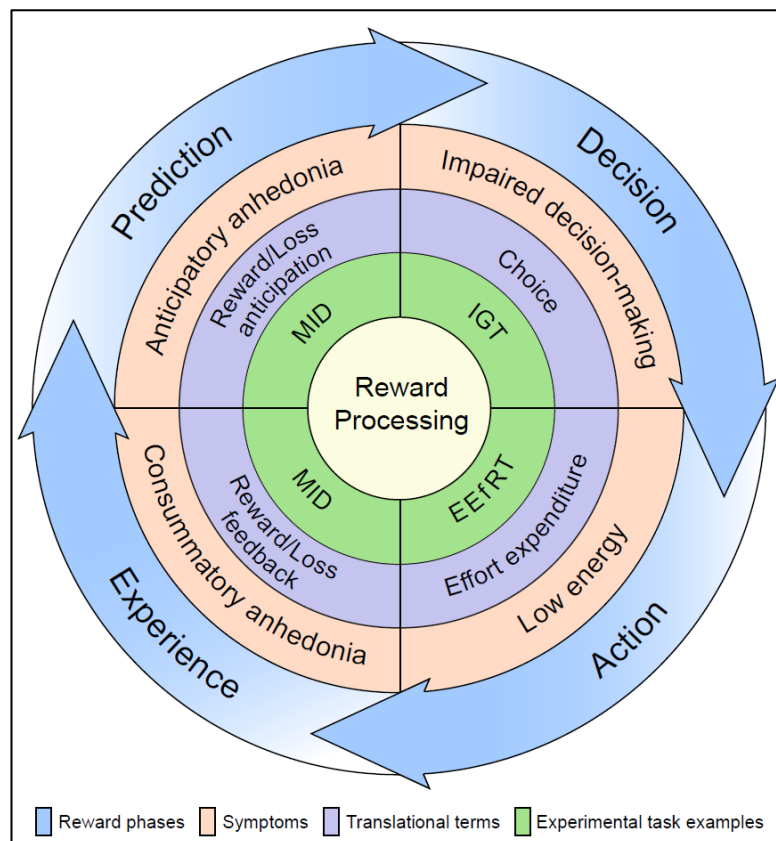


Figure 1.12. Illustration of the identified phases of reward and penalty processing and a mapping of these onto their associated clinical and translational terminologies. The outer layer (blue) demonstrates how these phases are linked in a continuous loop. Disruption of this cycle is thought to be associated with the common depressive symptoms identified in the next layer (orange). These symptoms are studied using translational concepts (purple), which are tapped into using experimental tasks such as the Monetary Incentive Delay (MID) task, the Effort Expenditure for Rewards Task (EEfRT) and the Iowa Gambling Task (IGT) (in green).

1.5.1 Data source and search strategy

We searched Pubmed, Scopus, PsychInfo and Web of Science for articles published in English from January 1, 2000 to February 1, 2017 using the following terms and their derivatives: depression, anhedonia, reward, motivation, reinforcement, punishment and aversion, prediction error, decision making and risk taking.

1.5.2 Detailed Inclusion and exclusion criteria

Inclusion criteria: Studies were required to provide a measure of depression or anhedonia in people with major depression disorder (MDD), at high-risk of depression (HR) or healthy controls (HC). We only selected studies that measured depression, or depressive symptoms, through questionnaires, structured interviews, or clinical diagnosis. In terms of reward paradigms employed, and following the classification described in Richards et al., (2013), we included instrumental-reward tasks and decision-making tasks, which require participants to complete an action correctly in order to obtain a reward (or avoid a penalty), being this action linked to the reward/penalty value in a trial-by-trial level. Hence, we excluded reward paradigms in which rewards/aversive stimuli were presented passively. Either positive (e.g. winning money) or negative (e.g. losing money) reward manipulations were permitted. No age restrictions were applied.

Exclusion criteria: Studies were excluded if they lacked a standard measure of depression. We excluded studies that measured depressive symptoms only in patients with another disorder (e.g. bipolar or schizophrenia, etc.), and did not include a depressed group also. This was done because our primary question concerns the effects of depression on reward processing and in the absence of a depressed control group, drawing inferences about such effects would be impossible. We also excluded studies in which reward processing was measured through non-experimental methods such as self-report measures or questionnaires. Furthermore, to guard against heterogeneity, we excluded studies in which physical punishment was delivered (e.g. heat, pain, electrical shock, etc.) as these are likely to engage different brain networks to receiving, for example, negative feedback. Similarly, studies were excluded if they employed passive exposure to pleasant/unpleasant stimuli such as facial emotions or images/tastes. For all studies, data extracted, if available, included design features of the studies and measurements. These are detailed in Table 1.3, 1.4, and 1.5.

1.5.3 Search Results

As shown in Figure 1.13, the initial search returned 58,401 studies; these were reduced to 26,492 after duplicates, as well as non-human and non-experimental studies, were removed based on keyword searches in EndNote (X7). Inter-rater reliability analysis based on 30 randomly selected articles showed a 97% of agreement across investigators. The final list included 171 studies; within those, there were 66 fMRI studies and 32 EEG studies and 73 studies employing mostly behavioural tasks or other methodologies. Data extracted, if available, were (a) type of study (observational or/and treatment study; cross-sectional or longitudinal), (b) sample characteristics (healthy, at-risk of depression (defined as the presence of either MDD in a parent, high depression scale scores in the absence of MDD diagnosis, or remitted MDD), depressed, or participants with other disorder; total sample size; percentage and sample size of depressed group; percentage of females in depressed group; percentage of medicated; mean, SD, and age range of depressed and comparison groups), and (c) methodology employed (behavioural, EEG, FC, or fMRI; reward task; depression measure; type of reward). Rewards were defined as monetary (i.e. the participant wins -or is led to believe they will win money based on performance), affective or primary. Additional data were extracted from papers that contained fMRI and EEG measures, as described below. Compared to reward processing, the neural bases of penalty processing have been far less studied in MDD.

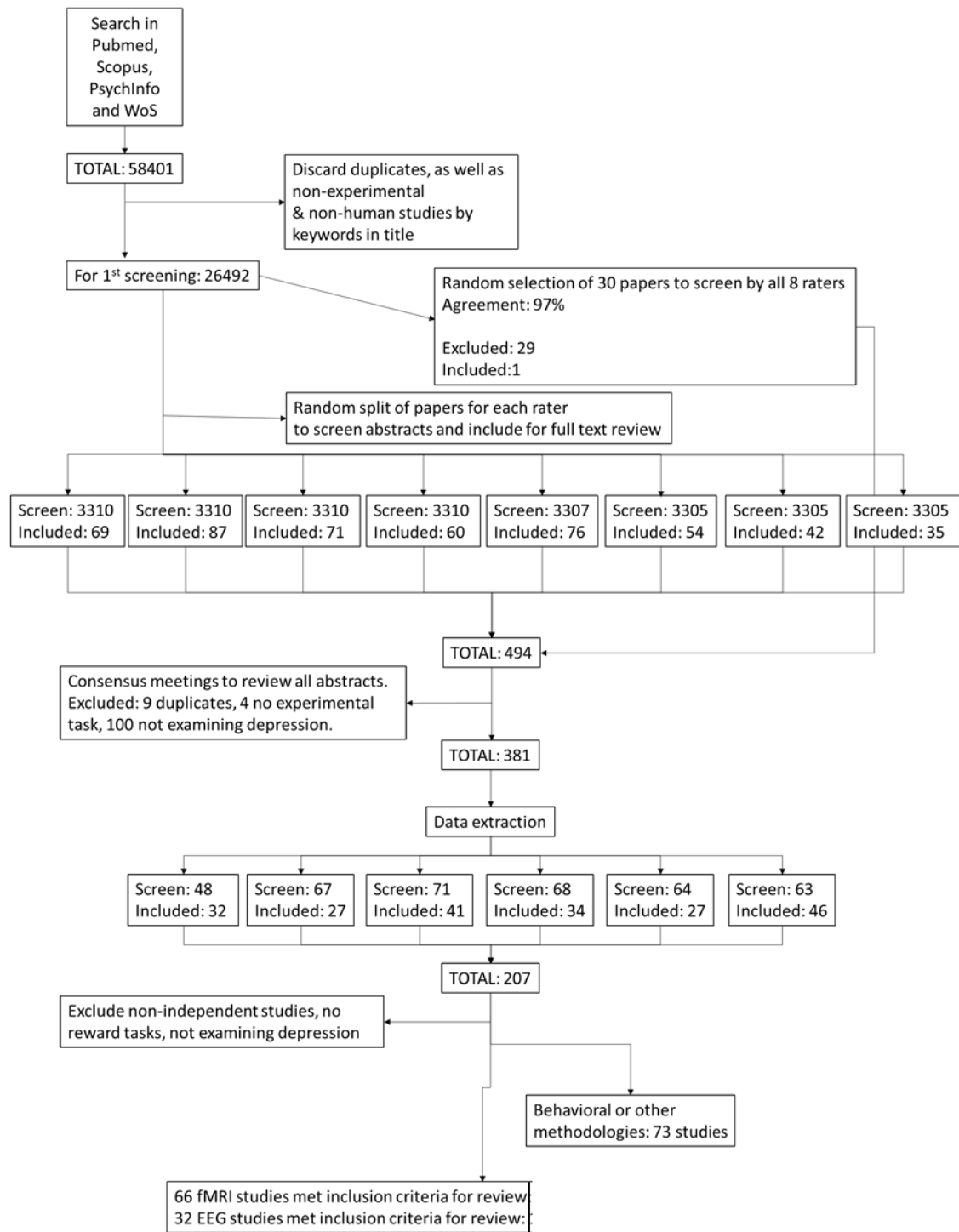


Figure 1.13. Search History

1.5.3.1 *Functional MRI studies*

For the fMRI studies, there were n=66 fMRI studies of which 50 reported coordinates for reward-related neural activity. Upon inspection of the studies, there were only a sufficient number of studies for the following contrasts: Reward Anticipation (mostly vs. baseline or vs. a neutral outcome); Reward Feedback (mostly vs. baseline or vs. a neutral cue); Loss Feedback + Loss Anticipation (mostly vs. a neutral cue /outcome). Therefore, we extracted the results of 38 studies (Admon et al., 2015; Arrondo et al., 2015; Casement et al., 2016; Chan et al., 2016; Chandrasekhar Pammi et al., 2015; Chung and Barch, 2015; Dichter et al., 2012; Dillon et al., 2014; Felder et al., 2012; Forbes et al., 2009; Forbes et al., 2010; Gorka et al., 2014; Gotlib et al., 2010; Gradin et al., 2011; Hagele et al., 2015; Johnston et al., 2015; Knutson et al., 2008; Luking et al., 2016; Mori et al., 2016; Olino et al., 2011; Olino et al., 2014; Pizzagalli et al., 2009; Redlich et al., 2015; Remijnse et al., 2009; Robinson et al., 2012; Rzepa et al., 2017; Satterthwaite et al., 2015; Schiller et al., 2013; Segarra et al., 2016; Sharp et al., 2014; Smoski et al., 2009; Smoski et al., 2011; Steele et al., 2007; Stoy et al., 2012; Stringaris et al., 2015; Ubl et al., 2015a; Ubl et al., 2015b; Yang et al., 2016). Sixteen studies were not included because they did not report on any of these contrasts or related variations (e.g. risky vs. safe choices, inequality vs. fairness). However, these 16 studies are referred to in the general discussion. Demographic information for the 32 studies with the relevant contrasts is presented in Table 1.3, and the methods and results are summarised in Table 1.4.

With reference to the distribution of studies in terms of group comparisons, a total of 24 studies used a case control design to compare people diagnosed with Major Depressive Disorder (MDD) and healthy volunteers (HV), 10 used non-depressed subjects at-risk of MDD (HR). A final group of 8 studies measured symptoms of depression continuously in subjects recruited from the community. Three of these studies belong to more than one definition.

In the following sections, I review the pattern of behavioural and neuroimaging (fMRI and EEG) findings which have emerged from the literature, and how such alterations may underlie or contribute to symptoms of depression.

Table 1.3. Demographic information for fMRI and EEG studies adhering to the inclusion criteria for results extraction.

Study	Sample Type	Age M(SD)	Total n	MDD/HR n	HV n	Female %	Medicated	Depression measure/s	Reward type	Task
<u>fMRI (N=32):</u>										
Admon et al. (2015)	MDD vs. HV	42.6(11.7) 37.7(14)	55	26	29	50	No	SCID, HAMD-21	Monetary	MID
Arrondo et al. (2015)	MDD vs. HV	33.08(9.15) 34.33(10.11)	67	24	21	32	Yes	PANS, BPRS, SANS, BDI, SHAPS, TEPS	Monetary	MID
Casement et al. (2016)	Depression on continuum	16(-)	123	N/A	N/A	100	-	KSADS, NRS	Monetary	Reward guessing task
Chan et al. (2016)	HR (high anhedonia score [^]) vs. HV	18.8(1.8)	28	8	20	71	No	CPAS, CSAS, TEPS	Affective	AID
Chandrasekhar Pammi et al. (2015)	MDD vs. HV	31.9(7.5) 27.5(2.4)	20	10	10	20	-	HADS	Monetary	Decision making task
Chung & Barch (2015)	Depression on continuum (anhedonia [^])	35.56(8.61)	27	N/A	N/A	44.4	-	SHAPS, BDI, Chapman Social and physical anhedonia	Monetary	Monetary reward paradigm
Dichter et al. (2012)	HR vs. HV	23.6(4) 27.9(6.3)	38	19	19	78	No	BDI	Monetary	MID
Dillon et al. (2014)	MDD vs. HV	34.3(12.1) 36.6(13.3)	42	21	21	50	No	BDI-II, SHAPS, MASQ	Monetary	Memory task
Felder et al. (2012)	Depression on continuum	23.3(4.3)	12	N/A	N/A	100	No	BDI-II	Monetary	Wheel of Fortune
Forbes et al. (2009)	MDD vs. HV	13.5(2.1) 13.1(2.6)	43	15	28	70	No	PANAS-C, MFQ, KSADS	Monetary	Card guessing
Forbes et al. (2010)	Depression on continuum	11.9(0.9)	77	N/A	N/A	50	No	PANAS-C, MFQ	Monetary	Event-related card guessing

Gorka et al. (2014)	MDD vs. HV	25.4(7.7) 29.5(13.1)	40	9	18	66.7	Yes	HAMD, IDAS	Monetary	Passive slot machine
Gotlib et al. (2010)	HR vs. HV	12.2(1.7) 12.6(1.4)	26	13	13	100	No	KSADS, CDS-I	Monetary	MID
Gradin et al. (2011)	MDD vs. HV	45.2(12.3) 40.6(11.8)	46	15	17	60	-	BDI, HAMD, anhedonia measured from a BDI derived subscale of items	Primary	Instrumental reward- learning task
Hagele et al. (2015)	MDD vs. HV + Depression on continuum	40.1(11.6) 37.7(11.1)	184	24	54	29.1	No	HRSD-21, BDI	Monetary	MID
Johnston et al. (2015)	MDD vs. HV + Depression on continuum	50.79(10.6) 46.14(13.97)	40	19	21	75	Yes	MINI PLUS, HAMD, HADS, MADRS, BDI, BHS	Accuracy	Modified Pessiglione reward task
Knutson et al. (2008)	MDD vs. HV	30.7(8.8) 28.6(4.2)	26	14	12	64.2	No	SCID	Monetary	MID
Luking et al. (2016)	HR vs. HV	9.2(1) 9(1.1)	48	16	32	50	No	CDIC, CBCL, CDIP	Monetary	Card guessing
Mori et al. (2016)	HR vs. HV	18.5(0.6) 19.1(0.7)	30	15	15	60	No	BDI-II	Monetary	MID
Olino et al. (2011)	HR vs. HV + Depression on continuum	13.3(2.4)	26	10	16	73.1	No	KSADS	Monetary	Card guessing
Olino et al. (2014)	MDD vs. HV	15.8(3) 15.5(2.5)	26	14	12	73.1	-	SCID	Monetary	Card guessing
Pizzagalli et al. (2009)	MDD vs. HV	43.1(12.9) 38.8(14.4)	61	30	31	42	No	SCID, HAMD	Monetary	MID
Redlich et al. (2015)	MDD vs. HV	38.4(12) 38.5(12.2)	67	33	34	51.5	Yes	SCID-IV, BDI, HAMD, SHAPS-D	Monetary	Card guessing

Remijnse et al. (2009)	MDD vs. HV	35(-) 32(-)	67	20	27	40	Yes	BDI, HAMD, MADRS	Monetary	Reversal learning task
Robinson et al. (2012)	MDD vs. HV	36(11) 31(6)	27	13	14	38	No	SCID	Affective	Pavlovian reward- punishment prediction
Rzepa et al. (2017)	HR vs. HV	16.6(1.2) 16.2(1.6)	33	16	17	75	No	MFQ	Primary	Taste
Satterthwaite et al. (2015)	Depression on continuum	38.8(12.8) 39.5(11.6)	77	22	32	44	Yes	BDI	Monetary	MID
Schiller et al. (2013)	HR vs. HV	23.6(4.1) 27.9(6.3)	38	19	19	78.9	No	BDI-II, RRS	Monetary	MID
Segarra et al. (2016)	MDD vs. HV	33.0(9.1) 34.3(10.1)	66	24	21	21.9	Yes	DSM-IV, SHAPS, BDI	Monetary	Simulated slot machine
Sharp et al. (2014)	MDD + HR vs. HV	13.3(1.8) 13.7(1.8)	52	33	19	100	-	SCID, MFQ, BDI, DISC-IV	Monetary	Card guessing
Smoski et al. (2009)	MDD vs. HV	34.8(14.3) 30.8(9.7)	29	14	15	50	No	HAMD	Monetary	Wheel of fortune
Smoski et al. (2011)	MDD vs. HV	34.4(15.1) 26.2(6.3)	22	9	13	-	Yes	BDI	Monetary, Affective	MID
Steele et al. (2007)	MDD vs. HV	45.9(10.7) 43(13.3)	29	15	14	62	Yes	BDI, STAI, SHAPS, HAMD	Accuracy	Gambling task
Stoy et al. (2012)	MDD vs. HV	41.9(12.2) 39.5(11.9)	30	15	15	33.3	Yes	HRSD	Monetary	MID
Stringaris et al. (2015)	MDD vs. HV + HR vs. HV	14.4(0.3) 14.4(0.4)	1576	22	123	86	Yes	DAWBA	Monetary	MID
Ubl et al. (2015)	MDD vs. HV	46(11.8) 43.9(12.8)	58	30	28	16	No	SCID, BDI-II, SHAPS, HAMD	Monetary	Modified version of a paradigm by Kirsch

Ubl et al. (2015)	HR vs. HV	41.1(12) 42.7(12.1)	46	23	23	53.3	No	BDI II, HAMD, SHAPS, SCID	Monetary	Monetary reward paradigm
Yang et al. (2016)	MDD vs. HV	28.9(7) 28.3(7.8)	50	25	25	50	No	HAMD, BDI	Monetary	EEfRT
<i>EEG (N=12):</i>										
Liu et al. (2014)	MDD vs. HV	30.7(10.1); 34.1(10.2)	54	27	27	74.1	Yes	BDI-II, HRSD	Monetary	Doors Guessing Task
Foti et al. (2014)	MDD vs. HV	26(8.9); 23.8(2.9)	76	34	42	100	No	MASQ	Monetary	Doors Guessing Task
Weinberg & Shankman (2017)	HR (remitted non- melancholic MDD) vs. HV	23(3.3); 21.8(2.9)	156	56	71	6	Yes	IDAS-II	Monetary	Gambling task
Mueller et al. (2015)	MDD vs. HV	31.4(11.1); 29.4(11.1)	42	22	20	61.5	Yes	BDI-II	Monetary	Gambling task
Webb et al. (2017)	MDD vs. HV	15.9(1.7); 15(1.6)	51	26	25	100	Yes	BDI-II	Monetary	Guessing task
Padrao et al. (2013)	High vs. low anhedonia^	22(2.3)	43	21	22	83.7	No	PAS	Points	Gambling task
Bress et al. (2013)	With and without MDE ⁺ by follow up	17.6(0.9); 17.8(0.9)	68	16	52	100	No	PHQ-9	Monetary	Reward guessing task
Nelson et al. (2016)	Depression on continuum	14.4(0.6)	444	N/A	N/A	100	Yes	Dysphoria subscale of the IDAS-II	Monetary	Doors Guessing Task
Bress, Meyer, & Hajcak (2015)	Depression on continuum	12.1(0.8)	25	N/A	N/A	48	-	CDI:T	Monetary	Doors Guessing Task

Bress, Meyer, & Proudfit (2015)	Depression on continuum	12.8(1.5)	71	N/A	N/A	-	-	CDI:T	Monetary	Doors Guessing Task
Bress et al. (2012)	Depression on continuum	10.6(1.6)	64	N/A	N/A	40.6	-	CDI:T	Monetary	Doors Guessing Task
Ait Oumeziane & Foti (2016)	Depression on continuum	23.6(10.3)	260	N/A	N/A	62.2	-	DASS-21	Monetary	Doors Guessing Task

- information not provided; ^A continuous measure of anhedonia; +MDE = major depressive episode; where possible, ages are presented separately for the depression and the HV group (the latter below).

Abbreviation of measures: BDI = Beck's Depression Inventory; BHS = Beck Hopelessness Scale; BPRS = Brief Psychiatric Rating Scale; CDI:T = Child Depression Inventory, total of child and parent reports; CDIP = The Cervical Dystonia Impact Profile; CDS = Cardiac Depression Scale; DASS = Depression, Anxiety, and Stress Scale; DAWBA = development and well-being assessment; HADS = Hospital Anxiety and Depression Scale; HAMD = Hamilton Depression Rating Scale; HRSD = Hamilton Rating Scale for Depression; IDAS = Inventory of Depression and Anxiety Symptoms; KSADS = Kiddie Schedule for Affective Disorders and Schizophrenia; MADRS = Montgomery-Åsberg Depression Rating Scale; MASQ = Mood and Anxiety Symptom Questionnaire; MFQ = Mood and Feelings Questionnaire; MINI = Mini International Neuropsychiatric Interview; NRS = Nutritional Risk Screening; PANAS-C = Positive and Negative Affect Scale for Children; PAS = Physical Anhedonia Scale; PHQ = Patient Health Questionnaire; RRS = Ruminative Responses Scale; SANS = Scale for the Assessment of Negative Symptoms; SCID = Structured Clinical Interview for DSM-IV Axis I Disorders; SHAPS = Snaith-Hamilton Pleasure Scale; STAI = State-Trait Anxiety Inventory; TEPS = Temporal Experience of Pleasure Scale.

Table 1.4. Summary of the methods and results of fMRI studies utilising reward and penalty (loss) anticipation contrasts and reward and penalty feedback contrasts.

Study	Whole brain results	Task condition contrasts	Brain regions of activity difference	
			MDD <HV HR<HV Decrease with depression	MDD >HV HR>HV Increase with depression
Admon et al. (2015)	Yes	Feedback: reward + loss > neutral	L caudate; R caudate	-
Arrondo et al. (2015)	No	Anticipation: reward > neutral	R accumbens; L accumbens	-
Casement et al. (2016)	No	Anticipation: reward > baseline	-	dmPFC
Chan et al. (2015)	Yes	Anticipation: reward > neutral	L thalamus; R insula; L thalamus/pulvinar	-
Chandrasekhar et al. (2015)	Yes	Anticipation: reward > loss (parametric modulation, decision phase)	-	R middle temporal cortex (p<0.001)
		Loss: Neural Loss Aversion (parametric modulation with loss values of feedback phase)	R anterior insula; R dorsal striatum (putamen); R parahippocampal cortex	L cuneus; R lingual gyrus; R middle occipital cortex; L VTA/midbrain; L lingual gyrus; R posterior cerebellum; L middle occipital cortex; R inferior occipital cortex; R lingual gyrus; L posterior cerebellum; R posterior cingulate cortex; R precuneus
Chung & Barch (2015)	No	Anticipation: reward > baseline	Lateral globus pallidus	-
Dichter et al. (2012)	Yes	Anticipation: reward > neutral	-	L caudate; R anterior cerebellum; R cingulate gyrus (anterior); L cingulate gyrus (anterior); R frontal gyrus (middle); R frontal orbital cortex; L occipital fusiform gyrus; R occipital fusiform gyrus; R paracingulate gyrus (anterior); L parahippocampal gyrus (anterior); L parietal lobule (superior); R precuneous cortex, lingual gyrus; R Supplementary motor cortex; R supramarginal gyrus (posterior); L

			supramarginal gyrus (posterior)	
		Feedback: reward > neutral	R angular gyrus; L central opercular cortex; R central opercular cortex; L cingulate gyrus (posterior); L frontal orbital cortex; R frontal orbital cortex; R frontal pole; L insular cortex; R intracalcarine cortex; L planum polare; L precentral gyrus; R Superior lateral occipital cortex; L supramarginal gyrus (anterior); R supramarginal gyrus (posterior); L temporal fusiform cortex (posterior); L temporal gyrus (posterior, superior); R temporal Pole; R thalamus; L thalamus; L precuneous cortex; L supramarginal gyrus (posterior)	-
Dillon et al. (2014)	Yes	Feedback: reward > neutral	R parahippocampal gyrus; VTA/SN	-
Felder et al. (2012)	Yes	Loss: feedback on non-win trials	L angular gyrus; R caudate; R cingulate gyrus (Posterior); R frontal gyrus (middle); L frontal gyrus (middle); R frontal gyrus (superior); L frontal gyrus (Superior); R inferior frontal gyrus, pars opercularis; L frontal pole; R occipital cortex (lateral, superior); L paracingulate gyrus; L postcentral gyrus; L precentral gyrus; precuneous cortex; L temporal gyrus (middle, posterior); R middle temporal gyrus	-
Forbes et al. (2009)	No	Anticipation: reward > baseline	L caudate head	R DLPFC; L DLPFC; L DLPFC
		Feedback: reward > baseline	L caudate head	L medial frontal gyrus (Brodmann's area 10); L DLPFC (Brodmann's area 9); R DLPFC (brodmann's area 9)
Forbes et al. (2010)	No	Anticipation: reward > baseline	-	medial frontal gyrus; anterior cingulate
		Feedback: reward > baseline	VS	-
Gorka et al. (2014)	Yes	Anticipation: reward > neutral	-	R dACC
Gotlib et al. (2010)	No	Anticipation: reward > neutral	L putamen; L insula	R insula
		Feedback: reward > neutral	R anterior cingulate gyrus; L posterior cingulate gyrus; L midcingulate gyrus; L putamen or lentiform nucleus; L anterior cingulate gyrus; R anterior thalamic nucleus; L	-

			anterior cingulate gyrus	
		Loss: anticipation loss > neutral + feedback loss > neutral	L lentiform nucleus or globus pallidus; L midcingulate gyrus; R caudate; L putamen	L cingulate gyrus
Gradin et al. (2011)	Yes	Anticipation: parametric modulation of the cue value, decision phase	R hippocampus; R posterior parahippocampal gyrus	-
		Feedback: Parametric modulation of the Reward Prediction Error + parametric modulation of reward value	L putamen; L nacc; R nacc; L caudate; R caudate & thalamus; midbrain; R hippocampus	-
Hagele et al. (2015)	Yes	Anticipation: reward > neutral	R VS; L VS; R ventral striatal	-
Johnston et al. (2015)	Yes	Feedback: reward > neutral	ACC; nACC; posterior cingulate	insula
		Loss: feedback loss > neutral	nACC	DRN hippocampus; amygdala; insula
Knutson et al. (2008)	Yes	Anticipation: reward > neutral	L superior frontal gyrus	L anterior cingulate; L precentral gyrus; R postcentral gyrus
		Feedback: reward > neutral	R MPFC; L insula; R putamen; L putamen; L superior frontal gyrus; L insula; L postcentral gyrus; L inferior parietal lobe	-
		Loss: feedback loss > neutral	L parahippocampal gyrus	-
Luking et al. (2016)	Yes	Feedback: reward > neutral	caudate body; L ventral putamen; R ventral putamen; L medial globus pallidus; R medial globus pallidus; parahippocampal gyrus; anterior insula; anterior insula	-
		Loss: feedback loss > neutral	caudate body; L ventral putamen; R ventral putamen; L medial globus pallidus; R medial globus pallidus; parahippocampal gyrus; anterior insula; anterior insula	-
Mori et al. (2016)	Yes	Anticipation: reward > neutral	-	L angular gyrus; R angular gyrus; R middle frontal gyrus; R Inf parietal lobe

		Loss: anticipation loss > neutral	L angular gyrus; L inferior frontal gyrus	-
Olino et al. (2011)	No	Anticipation: reward > baseline	caudate body	-
Olino et al. (2014)	No	Anticipation: reward > baseline	striatum	-
		Feedback: reward > baseline	striatum	-
Pizzagalli et al. (2009)	Yes	Anticipation: reward > neutral	L putamen, report voxel peak p-value); R occipitofrontal fasciculus; R middle occipital gyrus	R uncus/parahippocampal gyrus; R inferior frontal gyrus; L inferior frontal gyrus; R middle frontal gyrus; R middle frontal gyrus; L middle frontal gyrus; R subgenual cingulate; R superior temporal gyrus; L occipitofrontal fasciculus/cingulum; L inferior parietal lobule; R lingual gyrus; R cerebellum
		Feedback: reward > neutral	R caudate; R caudate; L caudate; L caudate; R insula; R insula; R inferior frontal gyrus; R middle frontal gyrus; R middle frontal gyrus; R middle frontal gyrus; L precentral gyrus; R rostral anterior cingulate; R dorsal anterior cingulate; L posterior cingulate; R middle temporal gyrus; L cerebellum; L cerebellum	L fusiform gyrus
		Loss: anticipation loss > neutral + feedback loss > neutral	R cerebellum; R caudate; L caudate; L thalamus; R inferior frontal gyrus; R middle frontal gyrus; L precentral gyrus; L posterior cingulate; R superior temporal gyrus; R middle temporal gyrus; L middle temporal gyrus; L inferior occipital gyrus	L insula; R medial frontal gyrus; L postcentral gyrus; dorsal anterior cingulate; R posterior cingulate; L middle temporal gyrus; L lingual gyrus; L precuneus; R cerebellum
Redlich et al. (2015)	No	Feedback: reward > neutral	nACC	-
Remijnse et al. (2009)	Yes	Feedback: reward > neutral	-	gyrus temporalis superior; gyrus precentralis; occipital; putamen
Robinson et al. (2012)	Yes	Feedback: unexpected reward (after learning)	R putamen; L mid-cingulate cortex; L mid-occipital cortex	-
Rzepa et al. (2017)	No	Feedback: reward > neutral	pgACC; vmPFC	-

	Yes	Loss: anticipation aversive taste > neutral + feedback aversive taste > neutral	MFG; IFG; frontal pole; PCC; ACC	-
	No		pgACC; pgACC; pgACC; vmPFC	-
Satterthwaite et al. (2015)	No	Feedback: reward > loss	posterior cingulate; R anterior insula; L ventral striatum; R ventral striatum; anterior cingulate	-
Schiller et al. (2013)	Yes	Loss: anticipation loss > no loss + feedback loss > no loss	L SFG; L IFG (pars triangularis); L SFG	-
Segarra et al. (2016)	Yes	Feedback: reward > neutral	medial frontal cortex; R VS OFC thalamus and midbrain; L lingual gyrus, occipital lobe; L OFC; R inferior and middle temporal gyri; R angular and supramarginal gyri, parietal lobe; L angular and supramarginal gyri, parietal lobe	-
Sharp et al. (2014)	Yes	Feedback: reward > baseline	R middle temporal gyrus; inferior frontal gyrus; R ventral striatum; R inferior frontal gyrus; R inferior parietal lobe; supramarginal gyrus; medial frontal gyrus; L cingulate gyrus	-
	No		R VS	-
Smoski et al. (2009)	Yes	Anticipation: reward > neutral	caudate; cingulate gyrus; L cingulate gyrus; R cingulate gyrus; R frontal gyrus (inferior, pars triangularis); L frontal gyrus; R frontal gyrus; frontal pole; hippocampus; lingual gyrus; L occipital cortex; R occipital cortex; occipital cortex lateral superior; occipital fusiform gyrus; L post central gyrus; L precentral gyrus; R precentral gyrus; L precuneous cortex; R precuneous cortex; R subcallosal; R temporal gyrus; temporal gyrus; temporal pole; L thalamus; R thalamus	parietal operculum cortex
		Feedback: reward > neutral	R thalamus; frontal gyrus; frontal gyrus; lingual gyrus; occipital; occipital cortex lateral superior	anuglar gyrus; cuneal cortex; frontal gyrus; occipital fusiform gyrus; precuneous cortex; R temporal pole; thalamus left
		Loss: feedback no win > neutral	frontal gyrus; frontal orbital cortex; amygdala; caudate; central opercular cortex; cingulate gyrus; frontal operculum; frontal pole; heschl's gyrus; R hippocampus; insular cortex; lingual gyrus; occipital cortex (lateral inferior); R occipital cortex (lateral, superior); parietal lobe; planum temporale; postcentral gyrus; precuneous cortex; putamen; subcallosal cortex; temporal gyrus; temporal pole; thalamus	frontal gyrus

Smoski et al. (2011)	Yes	Anticipation: reward > neutral	R frontal orbital cortex; R frontal pole/OFC; L hippocampus; R occipital pole; R subcallosal cortex	-
		Feedback: reward > neutral	R occipital fusiform gyrus; R occipital pole	-
Steele et al. (2007)	No	Feedback: reward > loss	R VS; L VS	
		Loss: feedback loss > reward	Medial frontal cortex	-
Stoy et al. (2012)	No	Anticipation: reward > neutral	R VS	-
		Loss: anticipation loss > neutral	R VS; L VS	-
Stringaris et al. (2015)	No	Anticipation: reward > neutral	R caudate head; R caudate; L caudate; R medial frontal gyrus; R superior frontal gyrus; L superior frontal gyrus; L middle frontal gyrus; L caudate head; L putamen; Right caudate head; R caudate	-
Ubl et al. (2015)	No	Anticipation: high reward > neutral	R VS; R middle OFC; L rostral ACC	-
		Loss: anticipation high loss > neutral	L rAcc	-
Ubl et al. (2015) (2)	No	Anticipation: reward > neutral	-	right frontal superior gyrus; right amygdala; left hippocampus
Yang et al. (2016)	Yes	Anticipation: high reward > low reward + reward > baseline	L anterior lobe; L caudate; L frontal lobe middle frontal gyrus; L parietal lobe supramarginal gyrus	

1.5.4 Behavioural results

Several types of paradigms have been used to probe how MDD patients process information in the context of reward or loss (Figure 1.12). Two broad conclusions have emerged from this literature, with depressed individuals (MDD and depressive symptoms by clinical interview/self-reported questionnaire) showing hyposensitive responses to rewards (positive feedback) and hypersensitive/maladaptive responses to penalties (negative feedback).

1.5.4.1 *Hyposensitivity to reward*

Depressed individuals generally show blunted responses to rewarding information which could reflect deficits in approach or appetitive systems (Eshel and Roiser, 2010). Depressed patients displayed blunted responsiveness to reward (but not to anticipated punishment or to nonreward or avoidance) (McFarland and Klein, 2009). Moreover, in probabilistic instrumental learning tasks, depression was associated with a failure to develop a response bias towards high-probability wins (Henriques and Davidson, 2000; Henriques et al., 1994; Pizzagalli et al., 2008b; Vrieze et al., 2013b). This may reflect indifference to reward in depression and a reduced capacity to modulate behaviour according to prior reinforcements. These impairments in reward-related behavioural responses correlated specifically with the severity of self-reported anhedonia, independently of overall depression severity (Chase et al., 2010; Steele et al., 2007; Vrieze et al., 2013b). Moreover, MDD patients have shown to be less willing to expend effort in order to receive high monetary rewards relative to healthy controls. They were also less able to effectively use this information about reward magnitude and probability to guide choice behaviour (Treadway et al. 2012). This finding has been replicated in tasks in which effort has been operationalised as number of button presses and strength of response on a handgrip (Clery-Melin et al., 2011).

However, there were also contradictory behavioural findings in depressed patients in the literature. Two paradigms are discussed in greater detail below, the Iowa Gambling Task (IGT) and delay discounting tasks. The IGT is a laboratory probe developed to measure decision-making under uncertainty and risk (Bechara et al., 1994). Some studies (Cella et al., 2010; Ding et al., 2016; Moniz et al., 2016; Must et al., 2006; Olie

et al., 2015) suggested that depressed adult participants with MDD adopt a more disadvantageous strategy on the IGT compared to age-matched controls; however, the opposite has also been reported in MDD (Smoski et al., 2008) and in those scoring high on depressive symptoms (Byrne et al., 2016, noted a positive correlation between IGT score and their depression scale). There are also studies that found no difference when comparing at-risk (Westheide et al., 2007) or depressed (Dalgleish et al., 2004; Jollant et al., 2016; Oldershaw et al., 2009) groups to healthy volunteers. Similarly conflicting results were found in delay discounting tasks which probe the tendency of people to discount rewards according to how distant they are in time (Odum, 2011). Indeed, significant associations between delay discounting and depression go in different directions. Lempert et al. (Lempert and Pizzagalli, 2010) found that anhedonic individuals tended to choose larger but delayed rewards, whereas Imhoff et al. (Imhoff et al., 2014), as well as Pulcu et al. (Pulcu et al., 2014), found delay discounting and depression to be significantly correlated.

1.5.4.2 ***Hypersensitivity and maladaptive responses to penalties***

In contrast to behavioural responses to reward outcomes, depressed individuals seem to show an opposite behavioural response pattern to loss events. There was converging evidence of heightened sensitivity to negative outcomes/feedback and biased information processing and representations that mediate choice behaviour, including preferential attention, planning, memory and self-referential processing towards negative information (Beck, 2008; Disner et al., 2011; Gotlib et al., 2010a; Grimm et al., 2009; Sylvester et al., 2003).

Indeed, MDD patients (Elliott et al., 1997a; Elliott et al., 1996) and remitted MDD patients (Santesso et al., 2008) showed rapid deterioration in performance following an error made on a previous trial, and this was correlated with depression severity (Elliott et al., 1996). In line with learned helplessness models, a catastrophic response to negative feedback may be related to perceived failure triggering further failure-related thoughts and impacting on subsequent actions and task performance (Seligman, 1972). Indeed, MDD patients are most sensitive to misleading negative feedback which could reflect a tendency to exaggerate the importance of uncertain or misleading negative information (Murphy et al., 2003). With a perceived lack of

control, future actions may be biased thereby leading to a cycle of learned helplessness (Seligman, 1972). Another potential explanation is that depressed individuals fail to use negative feedback to improve future performance (Elliott et al., 1997a; Steele et al., 2007). Individuals with high scores on the BDI were significantly less likely to adjust behavioural actions following error trials relative to participants with low BDI scores (Holmes and Pizzagalli, 2007). The authors suggested that this could reflect abnormalities in motivation or performance monitoring in addition to blunted responses to reinforcement (as opposed to hypersensitivity). However, in the next section we will see how this explanation may not be fitting in the context of neural findings of hyperactive responses to penalties. Taken together, depression seems to be related to maladaptive responses to penalty feedback, and various mechanisms could underlie this, including, hypersensitivity to punishment, failure to adapt and learned helplessness.

In summary, depression seems to be broadly associated with reduced expectation of future rewards, diminished ability to modulate behavior as a function of reward or penalty history, reduced willingness to exert effort in order to gain reward and hypersensitivity to negative feedback. However, some contradictory findings have been reported. The tendencies described above may cause or exacerbate depressive symptoms, as a failure to adapt behaviour to reinforcers may lead to less rewards and more penalties, in a self-maintaining vicious cycle.

1.5.5 **Functional MRI studies**

1.5.5.1 ***Reward anticipation and outcome***

Overall, for whole-brain and ROI analyses we found 24 studies comprising 32 experiments, 119 foci and 822 subjects for reward anticipation and 22 studies comprising 27 experiments, 135 foci and 572 subjects for reward feedback.

Cross-sectional studies

Adolescents and adults with depression were found to show altered responses in the ventral and dorsal striatum, and in frontal regions including the ACC, OFC, medial prefrontal cortex (MPFC) and middle frontal gyrus during *reward anticipation*,

relative to matched healthy controls (HC). The most consistent neural correlate of adolescent depression was reduced activation in the caudate (Forbes et al., 2006; Forbes et al., 2009; Olino et al., 2011) and this response persisted even following positive feedback (i.e. a win in the previous trial) (Olino et al., 2011). Reduced striatal activation was also reported in depressed adults in the caudate (Smoski et al., 2009; Zhang et al., 2013) and posterior putamen (Pizzagalli et al., 2009), although activation in the caudate has been more localised to the ventral caudate and NAcc in adult MDD as compared to adolescent MDD (Arrondo et al., 2015; Hagele et al., 2015; Luking et al., 2016c; Stoy et al., 2012a). The evidence relating depression and hypoactivity in frontal regions is mixed. Some studies showed that the MDD group had lower activity in inferior OFC (Forbes et al., 2006; Smoski et al., 2011), paracingulate cortex (Smoski et al., 2011), ACC (Smoski et al., 2009) and middle frontal gyrus (Smoski et al., 2009), whilst others reported higher activity in these regions (Casement et al., 2014; Forbes et al., 2009; Forbes et al., 2006; Gotlib et al., 2010a; Knutson et al., 2008; Ubl et al., 2015a). Thus, when depressed individuals are presented with cues anticipating rewards, a reduction in striatal activity is a more consistent finding, with alterations (increases or decreases) in prefrontal regions also being reported.

A prominent finding of the literature review was the association between depression, consummatory anhedonia, and blunted striatal responses to *reward outcomes* (Admon et al., 2015a; Forbes et al., 2009; Forbes et al., 2010; Gotlib et al., 2010b; Hagele et al., 2015; Knutson et al., 2008; Pizzagalli et al., 2009a; Segarra et al., 2016; Sharp et al., 2014; Yang et al., 2016). This is surprising as one might expect the outcome phase to report more inconsistent results as it is a complex period with multiple processes occurring simultaneously. These include the response to the reward itself (including information about its pleurability or value), evaluation against expectation, integration into memory and preparation for the next trial. Some studies also reported decreased or increased responses in frontal (Forbes et al., 2009; Remijnse et al., 2009; Segarra et al., 2016; Sharp et al., 2014) and limbic regions (Johnston et al., 2015; Smoski et al., 2009).

In sum, these fMRI findings fit with predictions based on animal work (Schultz et al., 1997) about the centrality of the striatum in reward processing. In light of prior evidence (see Section 1.3 on the neural circuitry of reward and penalty processing), reduced responsivity in the VS, caudate and putamen in MDD for reward anticipation

may represent dysfunctions in coding the incentive salience or magnitude of reward-related stimuli and the initiation of goal-directed actions. Altered responses in frontal regions (either higher or lower) implicate abnormal monitoring of incentive-based behavioural responses (OFC and middle frontal gyrus) and conflict monitoring (ACC). For the outcome phase, blunted striatal responses could reflect deficits in hedonic function. However, the dominant model of striatal dopamine activity is that the salience or anticipatory activity predicts the outcome in cued-reward tasks (Schultz, 2016). In this context, any blunting in anticipatory processing or reduction in salience of cues (associated with depressive illness), could also affect outcome processing. Accordingly, blunted striatal activation to reward outcomes could indicate weaker perceived action-outcome relationship and/or weaker responses to unpredictable rewards in depression.

However, when drawing inferences from these studies, it is important to be aware of their methodological and conceptual limitations. Several of the studies were conducted in clinic or convenience samples which are liable to selection, referral and Berkson type biases (Berkson, 1946; Sackett et al., 1979). This may give rise to spurious results particularly when effects of comorbidity were not assessed. Indeed, several studies included MDD patients with comorbid anxiety disorders and this makes it difficult to delineate the specificity of the findings to MDD. There was also a high prevalence of patients taking medication, which may confound neuroimaging findings given that some medications are associated with reduced activity in striatal regions (Eshel and Roiser, 2010; McCabe et al., 2009). Finally, the studies reviewed indicate the ‘state’ aspects of neural changes and cannot delineate whether reward alterations are a cause, correlate, or consequence of depression. Thus, studies on individuals at high risk for depression are required to understand whether anticipatory neural function is abnormal in individuals prior to depression onset and thus represents a vulnerability marker for future MDD. Indeed, depression is frequently transmitted across families from one generation to the other. Offspring of depressed parents have a three-to-five fold increased lifetime risk for developing MDD and thus represent a high risk (HR) population (Goodman, 2007; Rice, Harold and Thapar, 2002; Sullivan, Neale and Kendler, 2000). Prospective family risk designs in neuroimaging studies are explored below.

Longitudinal fMRI studies

We found nine longitudinal studies examining the link between depression and reward processing (Admon et al., 2015b; Carl et al., 2016a; Morgan et al., 2013; Morgan et al., 2016; Mori et al., 2016a; Stoy et al., 2012b; Stringaris et al., 2015c; Telzer et al., 2014; Walsh et al., 2016). Five of those studies were conducted as part of treatment trials (Admon et al., 2015b; Carl et al., 2016a; Mori et al., 2016a; Stoy et al., 2012b; Walsh et al., 2016), none of which included randomisation, placebo, or other control equivalent. Among the treatment modalities, three studies reported on behavioural activation (BA) and two used escitalopram, whereas five of the studies were observational (Admon et al., 2015b; Morgan et al., 2013; Morgan et al., 2016; Stringaris et al., 2015c; Telzer et al., 2014). As in the cross-sectional studies, the MID was the most commonly employed task; six out of nine studies used the MID (Admon et al., 2015b; Carl et al., 2016a; Mori et al., 2016a; Stoy et al., 2012b; Stringaris et al., 2015c; Walsh et al., 2016).

Decreased activation in the striatum when anticipating a reward was associated with subsequent depressive disorder and an increase of symptoms in observational fMRI studies that reported task activation during that phase (rather than during decision making or using a connectivity analysis) (Gotlib et al., 2010; Olino et al., 2014; Sharp et al., 2014). HR youth exhibited decreased activation in putamen and insula (Gotlib et al., 2010) and VS (Olino et al., 2014) during reward anticipation compared to a low risk (LR) group. This was true even when controlling for depressive symptoms and positive affect (Olino et al., 2014). Thus, these familial depression risk designs suggest that individual differences in reward function may lead some individuals over the lifespan to have reduced anticipatory responses to rewards, irrespective of episode status (i.e. trait marker). The contribution of the frontal cortex to depression, however, was not consistent (Morgan et al., 2013; Stringaris et al., 2015c). Four of the five longitudinal observational studies were conducted in adolescents. Two of these employed connectivity measures during win feedback: one found that accumbens-mPFC connectivity was positively correlated with a history of depression (Morgan et al., 2016), while the second reported that caudate-dACC connectivity was decreased in depression (Admon et al., 2015b). Further studies examining alterations in network integration, and connectivity analyses such as Dynamic Causal Modelling would be

useful in characterising the strength of the association between depression and abnormal fronto-striatal connectivity.

1.5.5.2 *Penalty anticipation and outcome*

Overall, for whole-brain and ROI analyses, there were only 13 studies (less than half than that reported for rewards) reporting activation changes for either loss anticipation or loss feedback.

Loss-related responses were predominantly localised to the striatum, insula, ACC, parahippocampus and amygdala (Admon et al., 2015a; Gotlib et al., 2010b; Luking et al., 2016a; Rzepa et al., 2017; Ubl et al., 2015a). This is in line with studies suggesting that penalty-related responses more robustly activate limbic and cortical regions involved in conflict monitoring (Botvinick et al., 2004; Gradin et al., 2011). For the anticipation of losses, there were mixed findings with some studies showing blunted (Admon et al., 2015a; Rzepa et al., 2017; Schiller et al., 2013; Stoy et al., 2012a; Ubl et al., 2015a) and others, increased (McCabe et al., 2009; McCabe et al., 2012) responses in depressed relative to healthy control subjects. In contrast, several studies reported elevated loss-related signals in the anterior and posterior cingulate, anterior insula, and striatum to losses or missed rewards (Admon et al., 2015a; Engelmann et al., 2017; Gotlib et al., 2010b; Luking et al., 2016b). This was suggested to reflect heightened sensitivity to negative outcomes. As mentioned above, responses in the outcome phase may not only reflect response to the penalty itself, but also evaluation against expectation. Thus, increased BOLD responses could represent a stronger perceived action-penalty outcome relationship and/or stronger responses to unpredictable negative outcomes in depression.

1.5.5.3 *Prediction error*

As detailed in Section 1.4, mathematical algorithms have also been used to give insights into the nature of brain signals during the processing of reinforcing stimuli. Although, this approach has still not been applied extensively in the study of

depression, in particular for penalty-related prediction error (PE) signalling, it is important to summarise the emerging trends.

The majority of studies in the literature review demonstrated reduced encoding of reward-related PE in several regions of the fronto-striatal-limbic reward circuit in depression (Gradin et al., 2011; Kumar et al., 2008; Rothkirch et al., 2017; Ubl et al., 2015a). Specifically, there was reduced reward-related PE in the ventral striatum (Gradin et al., 2011; Kumar et al., 2008; Ubl et al., 2015a), ACC (Kumar et al., 2008), medial OFC (Rothkirch et al., 2017), retrosplenial cortex (RC) (Kumar et al., 2008), midbrain (Gradin et al., 2011; Kumar et al., 2008) and hippocampus (Kumar et al., 2008). The degree of signal reduction in these regions correlated with syndrome and anhedonia severity (Gradin et al., 2011; Kumar et al., 2008; Rothkirch et al., 2017). Thus, impaired neural coding of reward-related PEs by depressed individuals could reflect attenuated neural resources for processing reward learning signals that can be linked back to blunted attention and salience processing of appetitive cues. In other words, the PE results may be consistent with diminished ability of depressed patients to use reinforcement to change behaviour (Section 1.5.4), with the most severely ill patients exhibiting the greatest abnormality.

In contrast to the reward PE findings, there was a relative paucity of research linking penalty-related PEs to depression. Whilst there is some evidence of enhanced encoding of penalty-related PE in the ventral striatum in depression relative to healthy volunteers (Ubl et al., 2015), there is also evidence of no group differences in penalty-related PE encoding in the striatum and insula (Rothkirch et al., 2017), and this may be related to medication status. The results of Ubl and colleagues suggest that penalty-related learning of stimulus-response-outcome associations in depression might be biased by increased salience attribution to stimuli (Berridge, 2007; Jensen et al., 2007). Such increased PE signalling may bias action selections and avoidance behaviour in loss-related events (Garrison et al., 2013). However, there is clearly a need for a replication of these results in medication naïve individuals.

1.5.5.4 *Explanation for discrepancies in findings*

As we have seen in the review, there are several sources which could lead to variations in the findings linking reward and penalty processes to depression. This can broadly be divided into individual differences, power issues, sample characteristics and differences in study and task design. Figure 1.14 provides a comprehensive overview of these factors.

For example, with regards to individual differences in the literature review, it is worth speculating about the fact that there was a lower heterogeneity in the younger than older age subsamples. The younger samples were more likely to be community-based, narrower in age range, and had lower levels of medication, whilst the older sample was more diverse in terms of demographic variables. Medication was often reported inconsistently and therefore we could not assess its effects on the outcomes. It should also be noted that for the fMRI analyses, the younger sample contained more females than the older sample, which may have influenced the results. There is also the overarching issue of power. Many of these studies had relatively small sample sizes which can result in elevated false positive and false negative results.

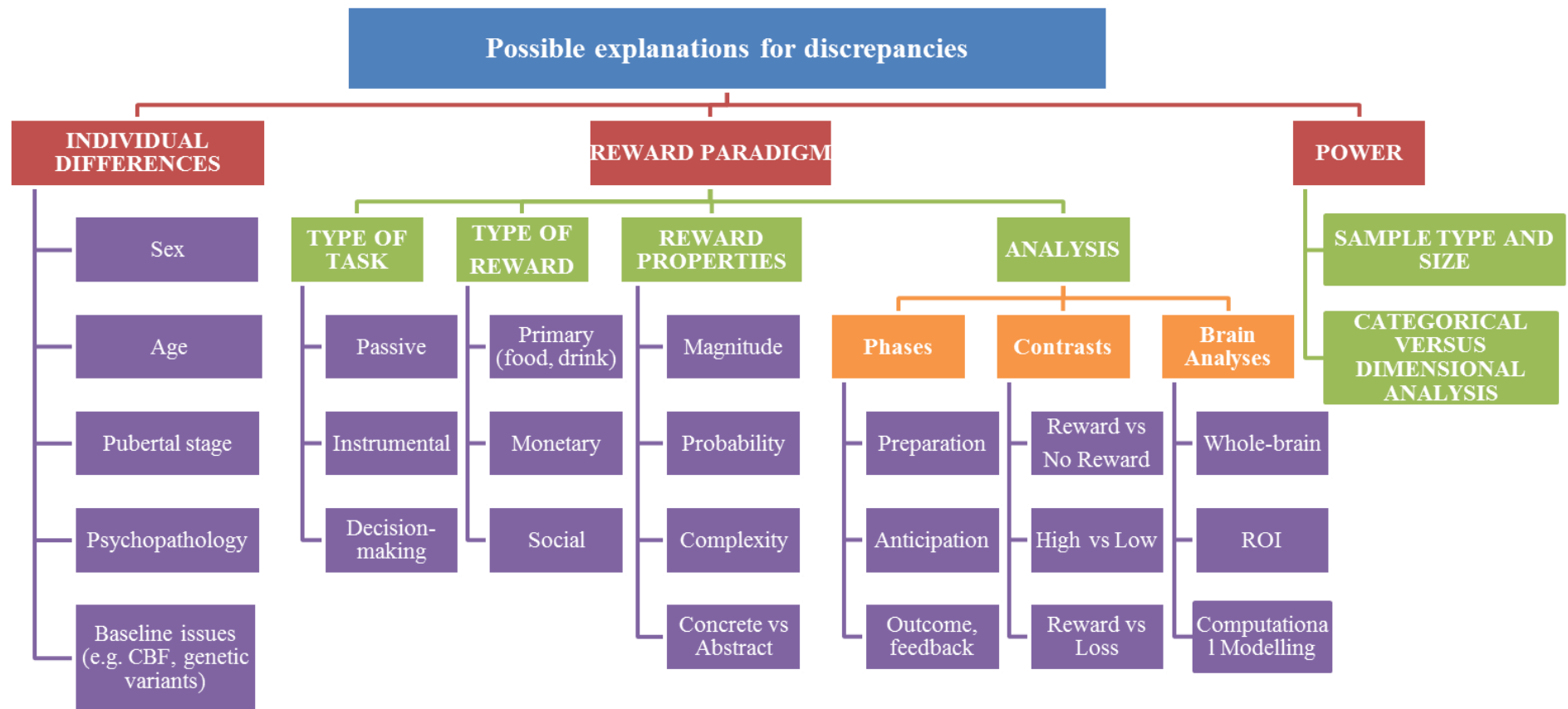


Figure 1.14. Schematic diagram summarising factors which may contribute to discrepant results across fMRI studies examining reward and penalty processing in depression.

1.5.6 **Electroencephalography (EEG) studies**

In contrast to fMRI, EEG studies provide millisecond temporal resolution. Event-related potentials enable a chronological delineation of reward-related activity by separating out the neural responses of anticipation and consummation with high precision (Banaschewski and Brandeis, 2007; Goldstein et al., 2006; Novak and Foti, 2015). Despite the limitations in spatial resolution, ERP methods are optimal for detecting subtle changes in the temporal dynamics of reward and penalty function.

The Feedback Negativity/Feedback-related negativity (FRN)² (also termed reward positivity (RewP) is an event-related potential which indicates the early appraisal of feedback (~300 ms after stimulus presentation at fronto-central recording sites) and appears larger following the presentation of negative feedback (Gehring and Willoughby, 2002; Hajcak et al., 2005; Holroyd and Coles, 2002b; Holroyd et al., 2004; Yeung et al., 2005). It was initially postulated that this ERP is not sensitive to absolute outcome values; rather, it reflects a measure of neural sensitivity to outcome valence (Foti et al., 2011a; Luck and Kappenman, 2011; Proudfit, 2015). However, more recently there is evidence that the FRN is also sensitive to variations in outcome magnitude (Sambrook and Goslin, 2015). Moreover, an FRN signal may be generated as neurons shift from encoding expected to actual outcomes (i.e. a Prediction Error signal) in the ACC (Hyman et al., 2017).

In terms of longitudinal EEG studies, in non-clinical and familial-depression risk samples, blunted RewPs during consumption of monetary reward was linked to increased depressive symptoms and prospectively predicted MDD (Bress et al., 2013; Bress et al., 2015a; Bress et al., 2012; Kujawa and Burkhouse, 2017; Nelson et al., 2016). Nelson and colleagues found that blunting of reward feedback at baseline was associated with, and predictive of, greater dysphoria at follow-up in a community-based sample of 444 adolescent girls (Nelson et al., 2016). Similarly, EEG recordings across two time points, two years apart, showed a stable association between blunted

² The RewP difference wave is calculated as gain minus loss difference, resulting in a fronto-central positivity (Novak et al., 2015). The FRN calculates the loss minus gain difference instead, resulting in fronto-central negativity. There is growing evidence that primarily reward-related activity following favourable outcomes elicits a relative positivity, supporting the RewP conceptualisation. The magnitude of the valence effect (win vs. loss) is the same in each case.

FRN and increased depression scores in children and young adolescents (Bress et al., 2015b; Bress et al., 2012). These findings were consistent with another study that found low baseline FRN amongst adolescents with increased symptoms of depression at a 21-month follow-up, even after controlling for baseline symptoms (Bress et al., 2013). No studies in the current review examined longitudinal associations between the FRN and depression in adult participants. Moreover, it is important to assess neural correlates in clinical samples. For example, FDR samples include participants who will remain healthy or develop adolescent or adult-onset depression and these two conditions differ in terms of course, symptomatology, neural substrates and/or vulnerability factors.

A recent study was the first EEG study to decompose both anticipatory and consummatory phases of reward and penalty processing within the framework of the MID task in MDD (Landes et al., 2018). This found that MDD adolescents had delayed neural processing of reward cues, as indexed by a prolonged cue-P3 latencies, relative to controls. During the outcome phase, the MDD group had shorter feedback-P3 latencies in the reward versus punishment condition, and this was not found in the comparison healthy control group. The authors suggested that this could reflect delayed allocation of attentional resources to reward predicting cues in adolescent MDD as a result of monetary rewards being less motivationally relevant (Landes et al., 2018).

Taken together, and in line with the fMRI studies, these EEG results suggest a decreased brain sensitivity to anticipating and consuming rewards in depression. Whilst fMRI studies suggest this deficit to involve the striatum, the source of the FRN is still debated; however, it may partially reflect striatal signals (Carlson et al., 2011; Foti et al., 2011b), or the indirect influence of striatal signals on other neural regions (Holroyd and Coles, 2002a; Luu et al., 2003)

Table 1.5. Summary of the methods and results of the EEG studies adhering to the inclusion criteria.

Paper	Electrode	Mean amplitude window	HP filter	LP filter	EEG net	Signal measured (feedback contrast):	Main finding reported for the relationship between depression and the FRN/RewP:
Liu et al. (2014)	FCz	250-350	0.1	30	-	FRN (loss – gain)	MDD: M= -0.66, SD= 4.67 HV: M= -7.89, SD= 4.91
Foti et al. (2014)	Fz, FCz	250-350	0.01	30	Custom cap and the ActiveTwo BioSemi system	FRN (loss – win)	MDD: M= -2.69, SD= 4.39 HV: M= -4.9, SD= 3.43
Weinberg & Shankman (2017)+	Cz, FCz	220-360	0.1	30	ActiveTwo BioSemi system	FRN (loss – gain)	At risk (remitted non-melancholic MDD): M= -4.43, SD= 6.23 HV: M= -4.27, SD= 5.04
Mueller et al. (2015)+	FCz, Cz	250-400	0.5	50	ActiveTwo BioSemi system	FRN (negative – positive)	MDD: M= -.09, SD= 1.98 HV: M= 0.38, SD= 2.78
Webb et al. (2017)+	FCz	250-350	0.1	30	HydroCel Geodesic Sensor Net	FRN (loss – win)	MDD: M= -4.71, SD= 6.83 HV: M= -3.31, SD= 6.44
Padrao et al. (2013)+	Fz	260-310	0.01	70	-	FRN (loss – gain)	High anhedonia: M= -6.31, SD= 3.75 Low anhedonia: M= -5.9, SD= 4.77
Bress et al. (2013)	Fz, FCz	250-350	-	104	Custom cap and the ActiveTwo BioSemi system	FRN (loss – gain)	With MDE at follow up: M= -2.32, SD= 8.97 Without MDE at follow up: M= -5.9, SD= 9.76
Nelson et al. (2016)+	FCz	250-350	0.1	30	ActiveTwo BioSemi system	RewP (gain – loss)	r = -0.133
Bress, Meyer, & Hajcak (2015)	Fz, FCz*	275-375	0.1	30	ActiveTwo BioSemi system	FRN (loss – gain)	r = 0.54
Bress, Meyer, & Proudfit (2015)	Fz	275-375	0.1	30	ActiveTwo BioSemi system	FRN (loss – gain)	r = 0.41
Bress et al. (2012)	Fz, FCz, Cz*	275-375	0.1	30	ActiveTwo BioSemi system	FRN (loss – gain)	r = 0.38
Ait Oumeziane & Foti (2016)	Fz, Cz, FC1, FC2*	260-310	0.01	30	ActiCAP and the actiCHamp system	RewP (gain – loss)	r = 0.02

- information not provided; * = electrodes were pooled, + = authors were contacted and provided data

Table 1.6. EEG studies with FRN/RewP findings that were excluded.

Paper	Sample	N	Age	Task	Finding	Contacted	Reason for exclusion
Foti et al. (2011)	High familial risk for MDD vs. low (female only)	81	Adolescent	Doors Guessing Task	Post induction sadness rating was positively associated with the FN in high but not low risk participants	No	The longitudinal follow up from this study was included instead as it differentiated between participants who did/did not have a subsequent MDE and made group comparisons
Belden et al. (2016)	MDD vs. HV	78	Children	Doors Guessing Task	Depressed had a smaller response to rewards compared to control. No difference to losses	No	Sampled from the Pz electrode
Foti & Hajcak (2009)	Healthy	85	Young adults	Doors Guessing Task	Positive correlation between the FN (TF3/SF1 PCA component) and the DAS-21	No	PCA
Whitton et al. (2016)	rMDD vs. HV	60	Adults	Probabilistic reward task	Reward-related neural activity, derived from PCA, was reduced in remitted depressed participants, relative to controls	No	PCA
Weinberg et al. (2015)	Healthy, enriched for internalizing symptomology, plus a sibling pair	140	Adults	Doors Guessing Task	Neural response to rewards did not differ between siblings with and without a history of MDD	No	PCA
Foti et al. (2015)	Healthy	88	Young adults	Doors Guessing Task	Higher depressive symptoms were associated with blunted FN-Delta activity but not FN-Theta activity	No	PCA
Ruchow et al. (2004)	MDD vs. HV	32	Adults	Eriksen Flanker with monetary gains and losses based on performance	Controls had a more negative response to errors following errors compared to correct following an error, whereas depressed didn't demonstrate this difference	Yes	Peak extraction and conducted a trial n-1 analysis
Santesso et al.	Healthy	29	Young	Monetary	Higher negative emotionality	Yes	Peak extraction

(2012)			adults	Incentive Delay task	(combined BDI-II and PANAS NA scales) was associated with a more negative response to penalties		
Santesso et al. (2008)	rMDD vs. HV	27	Adults	Probabilistic punishment task	Found a larger negative deflection for the remitted MDD group, compared to control	Yes	Peak extraction
Tucker et al. (2003)	MDD vs. HV	47	Adults	‘Spatial Compatibility Task’	Diagnosis x Feedback interaction. Negative feedback conditions elicited a greater negative wave compared to positive in controls, whereas the most negative feedback differed from positive and moderately negative feedback in the depressed group.	Yes	Separated feedback types – no means for loss minus gain provided
Thoma et al. (2015)	MDD vs. HV	34	Adults	Feedback learning tasks: active and observational	The amplitude was reduced in MDD compared to control, across learning and feedback types	Yes	Combined feedback types – no means for loss minus gain provided

1.5.7 **Summary using the Bradford Hill Causality Criteria framework**

In summary, at a behavioural level, depression seems to be characterised by reduced expectation of future rewards, diminished ability to modulate behaviour as a function of reward or penalty history, reduced willingness to exert effort in order to gain reward and hypersensitivity to negative feedback. This behavioural phenotype may correspond to alterations in function in a network of fronto-striatal brain regions innervated by monoamines. The most consistent neuroimaging finding related depression to blunted striatal signals during reward feedback. There were also trends linking reduced striatal responses during reward anticipation to depression and in particular, the cardinal symptom of anhedonia, and the prediction of subsequent depressive disorder. There were comparatively fewer studies utilising paradigms that probe loss anticipation and feedback. Among these studies, there were mixed findings for the relationship between penalty anticipation and depression, with some studies showing blunted, and others, increased responses to penalty cues in depressed relative to healthy control subjects. Heightened sensitivity to negative outcomes in depression may be reflected by elevated loss-related signals in the ACC, anterior insula, and striatum.

Thus, the evidence from case-control studies, familial depression risk and prospective studies suggest that neurocognitive processes of reward and penalty processing are central to depressive risk and the depression phenotype. Sir Bradford Hill described the aspects of an association that need to be considered when deciding whether the likely interpretation of any association is causation (Hill, 2015; Höfler, 2005; Holt and Peveler, 2006). These are summarised in Table 1.7 with reference to examples in the literature reviewed here.

Table 1.7. Explanation of the Bradford Hill criteria for determining whether an association is causative. Adapted from Hill, (2015), Hofler, (2005) and Holt and Peveler, (2006).

Criteria	Meaning	Evidence for the association between the behavioural and neural correlates of reward/penalty processing and Depression
Strength of association	<i>A strong association is more likely to have a causal component than is a modest association.</i>	<ul style="list-style-type: none"> • The majority of published studies show an effect. See meta-analyses (Keren et al., 2018, in press; Zhang et al., 2013). • Effect sizes for associations between reward/penalty processing and depression are small. More precise associations, e.g. with specific symptoms rather than overall illness severity, or model based derivation of neural correlates, may show stronger associations.
Consistency	<i>The results have been replicated by different researchers and under different conditions.</i>	<ul style="list-style-type: none"> • Mixed findings across reward and penalty anticipation and outcome. • Most consistent results for reward outcomes. <p>E.g: (Admon et al., 2015a; Forbes et al., 2009; Forbes et al., 2010; Gotlib et al., 2010b; Hagele et al., 2015; Knutson et al., 2008; Pizzagalli et al., 2009a; Segarra et al., 2016; Sharp et al., 2014; Yang et al., 2016).</p>
Specificity	<i>A factor influences specifically a particular outcome or population.</i>	<ul style="list-style-type: none"> • Reward and penalty-related behaviours and fronto-striatal brain activation specific to (i) depression (not comorbid anxiety) and (ii) anhedonia. <p>E.g: (Elliott et al., 1997a; Forbes et al., 2006; Pizzagalli et al., 2009a; Stringaris et al., 2015a).</p>
Temporality	<i>The factor must precede the outcome it is assumed to affect.</i>	<ul style="list-style-type: none"> • Responses during reward anticipation and outcomes predict depression onset. <p>E.g: (Bress et al., 2013; Nelson et al., 2016; Sharp et al., 2014; Stringaris et al., 2015a).</p>
Biological	<i>The outcome increases</i>	<ul style="list-style-type: none"> • Reward and penalty-related behaviours and fronto-striatal brain activation linked

gradient	<i>monotonically with increasing dose of exposure or according to a function predicted by a substantive theory.</i>	to dimensional measures of anhedonia and depression severity. E.g: (Admon et al., 2015a; Holmes and Pizzagalli, 2007; Stringaris et al., 2015a; Vrieze et al., 2013b).
Plausibility	<i>There is a credible scientific mechanism that can explain the association.(i.e. the observed association can be plausibly explained by substantive knowledge (e.g. biological) explanations.</i>	<ul style="list-style-type: none"> • Dimensional measures of anhedonia and depression severity and impaired reinforcement learning are associated with reward and penalty-related fronto-striatal brain activation and monoamine function. E.g: (Admon et al., 2015a; Holmes and Pizzagalli, 2007; Kumar et al., 2008; Rothkirch et al., 2017; Stringaris et al., 2015a; Vrieze et al., 2013b).
Coherence	<i>The association should not conflict with present substantive knowledge. It is like face validity.</i>	<ul style="list-style-type: none"> • Coherence within the behavioural and neuroimaging literature is good. E.g behavioural: (Henriques and Davidson, 2000; Henriques et al., 1994; Pizzagalli et al., 2008b; Vrieze et al., 2013b). E.g neuroimaging: (Admon et al., 2015a; Forbes et al., 2009; Forbes et al., 2010; Gotlib et al., 2010b; Hagele et al., 2015; Knutson et al., 2008; Pizzagalli et al., 2009a; Segarra et al., 2016; Sharp et al., 2014; Yang et al., 2016). • Incoherence arises between levels of understanding, i.e. the extent to which behaviour concurs with neural correlates of reward/penalty processing.
Experimental evidence	<i>Causation is more likely if evidence is based on randomised experiments. An intervention shows results consistent with the association.</i>	<ul style="list-style-type: none"> • Further studies needed (see Section 1.6, Table 1.8 and Table 1.10 for pharmacological and psychological intervention studies).
Analogy	<i>There are similar results we can draw a relationship to.</i>	<ul style="list-style-type: none"> • A potential analogy is the relationship between fear/anxiety and evolutionarily-preserved threat networks.

When considering these findings, the following conceptual and empirical challenges must also be considered.

First, postulating depression to be a generalised inability to anticipate or perceive pleasure (or avoid pain) may be overly simplistic. Depressed individuals can still crave rewards, as evidenced by the increased levels of drug and alcohol dependency in depression (Conway et al., 2006). We have found that reward anticipation deficits in depression were specific to anhedonia and not present in those with low mood only (Stringaris et al., 2015c). Anhedonia is a core feature of depression closely linked to reward processing (Zhang et al., 2016). Unfortunately, very few studies included measures of anhedonia to quantify the degree to which reward system dysfunction was moderated by levels of anhedonia. Future studies should use anhedonia measures alongside depression symptoms to address this question. It should also be noted that differential patterns of response to primary rewards have been found for depressed patients with different constellations of appetite symptoms (decreases vs increases in appetite amongst those depressed) (Lamers et al., 2017; Simmons et al., 2016). It is therefore possible that reward aberrations do not affect all depressed patients, or are not present throughout the course of the illness. Further studies that examine reward processing in relation to these specific symptoms will be helpful. Moreover, the improved temporal resolution afforded by electrophysiological measures (EEG/MEG) has not been fully exploited in prior studies linking reward processing and depression. Depression studies that combine the high temporal precision of EEG/MEG with the spatial precision of fMRI are needed.

Second, the empirical association between brain and behaviour findings in reward processing in depression remains unsatisfactory. We found that most purely behavioural studies report a significant relationship between reward processing and depression. Very few studies demonstrate aberrations in depression that span the three levels of explanation: brain circuit, task behaviour, and clinical symptom.

Third, there were surprisingly few experimental studies embedded in treatment studies, thus limiting causal inferences about the role of reward processing in depression. Whilst some pharmacological (Admon et al., 2016; Lally et al., 2015; Stoy et al., 2012b) or psychological (Rice et al., 2015) interventions show promise in probing reward signal, they do not yet demonstrate that affecting reward mediates

depressive symptoms. The following section of the introduction will thus explore the modulation of reward and penalty processing by intervention in further detail.

1.6 Intervention studies

1.6.1 Antidepressant Drugs

Since the serendipitous discovery of the first clinically useful antidepressant drug (Ban, 2006), a range of antidepressant drugs have been developed that, with few exceptions, act to increase transmission of monoamines. It was hypothesised that acute monoamine potentiation (i.e. increasing the synaptic concentration of monoamines, such as serotonin) was the central mechanism of antidepressant action (Ross and Renyi, 1969). However, blockade of transporters can be detected within hours after drug administration, whilst clinical improvement requires days or weeks (Taylor et al., 2006; Vetulani and Sulser, 1975). The discrepancy in the neurochemical and therapeutic effects of antidepressants subsequently led to various theories which attempt to explain the delay in antidepressant drug efficacy in depression.

It is useful to refer to three perspectives (or levels of explanation) for the mechanisms of antidepressant drug action: neurochemical, neuroplastic and neurocognitive theories (Harmer et al., 2017).

First, neurochemical theories have been informed by animal models, human MRI and post-mortem studies and focus on intercellular mechanisms such as neurochemical, cellular and molecular processes. Neuroadaptive changes occur over days to weeks after the initiation of antidepressant treatment, thereby mirroring the delayed therapeutic effect of antidepressants (Sugrue, 1983). However, in recent years, there has been a shift from an exclusive focus on the neurochemical theories of antidepressant drug action to a broader conceptualisation of the effects of antidepressants on neuroplasticity and emotional-cognitive function. Second, mechanisms of neuroplasticity (such as pre and post-synaptic signalling, number and function of synapses, gene expression) are a fundamental process that underlie learning and memory as well as the ability of neuronal circuits to adjust to the external environment and subsequently make adaptive responses to future related stimuli (Citri and Malenka, 2008). Antidepressants promote synaptic plasticity in animal experimental studies by reversing or blocking the synaptic deficits caused by chronic stress (Bessa et al., 2009a, b; Duman and Aghajanian, 2012; Karpova et al., 2011; McEwen et al., 2015; McEwen and Morrison, 2013). The actions of SSRI and

norepinephrine reuptake inhibitor drugs on synapse number are subtle and delayed (Bessa et al., 2009a, b). Third, the neuropsychological theory enters the area of clinical psychology because it examines how antidepressants modify emotional processes, both at a neural and cognitive level. In contrast to neurochemical theories, neuropsychological effects of antidepressant drugs occur early, before changes in mood, yet are related to later clinical change (Harmer and Cowen, 2013; Harmer et al., 2017). The extent to which the psychological changes relate to the effects of synaptic plasticity (i.e. whether these reflect similar, parallel or dependent processes) remains unclear, as research to date has not addressed this question directly.

The main focus of the section below is on the third theory: the effects of antidepressant drugs on core psychological processes important in depression (Figure 1.15). I begin by describing how antidepressants alter negative bias; evidence which led to the formation of the cognitive neuropsychological model of antidepressant drug action (Harmer and Cowen, 2013). I then describe how similar experimental medicine approaches have been applied to the investigation of reward processing and their modulation by antidepressant drugs in depression, which is the focus of this thesis.

1.6.2 Cognitive neuropsychological model of antidepressant action

1.6.2.1 *Normalisation of negative emotional biases by antidepressants*

Catherine Harmer's group have pioneered a research strategy that focuses on key neuropsychological factors that maintain depression (e.g. negative affective biases) and the modification of which occur shortly after antidepressant treatment (Harmer, 2013). This approach provides an experimental medicine model by which psychological and pharmacological processes in depression can be assessed, integrated and understood.

Antidepressants lead to behavioural changes that are opposite to those seen in the depressed state and that resemble healthy controls. This process of remediation of negative biases in emotional processing has been termed '*normalisation*'. Specifically, double-blind randomised controlled studies in healthy volunteers show that acute and short-term (7-day) administration of serotonin reuptake inhibitor (SSRI) and

noradrenaline reuptake inhibitor antidepressants (citalopram, reboxetine, duloxetine, agomelatine and mirtazapine) reduce negative emotional processing compared to placebo treatment (Arnone et al. 2009; Harmer et al. 2003, 2004, 2008, 2011b). These antidepressants were found to increase the perception of ambiguous faces as happy and the recall of positive self-referent words in both healthy volunteers (Harmer et al., 2003a; Harmer et al., 2003b; Harmer et al., 2004) and depressed patients (Harmer et al., 2009c; Walsh et al., 2017) compared to placebo. An important observation is that the mechanism of the placebo response is not the same as the drug response, as placebo treatment does not affect emotional bias compared to a non-treatment group (Huneke et al., 2017).

Such behavioural changes are also associated with altered patterns of neural response. The amygdala over activity seen in depression to negative affective stimuli (Victor et al., 2010) is normalised (i.e. reduced) after one-week antidepressant treatment (Godlewska et al., 2012) and a similar reduction in amygdala response has been found in healthy volunteers early in treatment (i.e. after a single dose and 7 day regimen with SSRIs and NRIs) (Del-Ben et al., 2005; Harmer et al., 2006; Norbury et al., 2007; Murphy et al., 2009a; Rawlings et al., 2010; Windischberger et al., 2010). Importantly, changes in emotional processing biases and their neural correlates occur independently from changes in subjective mood (Harmer et al., 2009b). This suggests a direct effect of antidepressant drug treatment rather than a secondary consequence of changes in mood and affect. Thus, a cognitive neuropsychological model of antidepressant drug action (Harmer and Cowen 2013; Harmer, Goodwin and Cowen, 2009) postulates that antidepressants may act to restore the balance between positive and negative emotional processing early in treatment, prior to mood improvement (Harmer and Cowen, 2013; Harmer et al., 2009a; Pringle et al., 2011; Roiser et al., 2012).

Indeed, early changes in the perception and neural response to happy faces during antidepressant treatment is associated with subsequent improvement in clinical symptoms (i.e. predict later clinical response) (Godlewska et al., 2016; Shiroma et al., 2014; Tranter et al., 2009). For example, depressed patients who respond to six week escitalopram treatment show a greater reduction in neural response during the processing of negative versus positive facial expressions early (7 days) in antidepressant treatment (Godlewska et al., 2016). Moreover, early changes in affective processing are maintained during long-term treatment, with depressed

patients showing reduced responses in the amygdala and ACC to negative stimuli and increased responses to happy faces (Fu et al., 2007; Fu et al., 2004; Ma, 2015).

In order to explain the translation of rapid change in negative bias by antidepressants into clinical response, Harmer and colleagues suggest the following mechanism. Positive re-biasing of non-conscious processes by antidepressants may lead to changes in how stressors, life events and interpersonal interactions are managed and remembered. This process may involve re-learning a range of emotional associations, which would inevitably involve time and experience of life in the context of new processing biases. In line with this view, the association between early change in positive processing and a decrease in depression severity is moderated by interpersonal factors (perceived level of social support) (Shiroma et al., 2014).

In summary, the cognitive neuropsychological model of antidepressant action suggests that antidepressant drugs have ‘bottom-up’ effects on emotional processing which become translated into improved mood and conscious appraisal over time and with exposure to a real-world environment (Figure 1.15). This model raises interesting questions about whether therapeutic efficacy could be improved by pharmacological agents and psychological treatments that target key neural mechanisms or ‘biomarkers’ in depression. Indeed, it provides the opportunity for psychological-pharmacological combination strategies (e.g. introducing specific behavioural experiments at a time in which the individual may be most responsive to re-learning biases), rather than putting two rational treatments together. Put simply, this approach provides an experimental medicine model to generate specific predictions about treatment development (i.e. “rational treatment advances”), which are vital for psychiatric diseases where treatment options are limited and unsatisfactory like in depression (DePaulo, 2006).

The testability of the model is thus a key advantage, and a number of questions remain unanswered. There is a need to further characterise how antidepressants working on different neurotransmitter systems impact upon affective processing and predict clinical response in larger samples. This may have implications for stratified/personalised medicine, where treatment is tailored towards the predominant symptomatology for an individual MDD patient (Korte et al., 2015). Further work is also needed into how interpersonal environment leads to changes in strategic

processing, perhaps by studies using ecological monitoring of everyday experiences. A more pressing challenge for the model is to characterise how changes in negative bias are related to plasticity. It is currently difficult to examine the inter-dependence and time scale of changes in plasticity and bias in the same individual because of the absence of reliable neural plasticity markers in vivo in humans. Thus, Harmer and colleagues suggest that the development of animal models of emotional bias, (which show similar antidepressant drug effects to human studies) will be necessary for exploring the potential synergistic effects of plasticity and negative bias (Harmer et al., 2017).

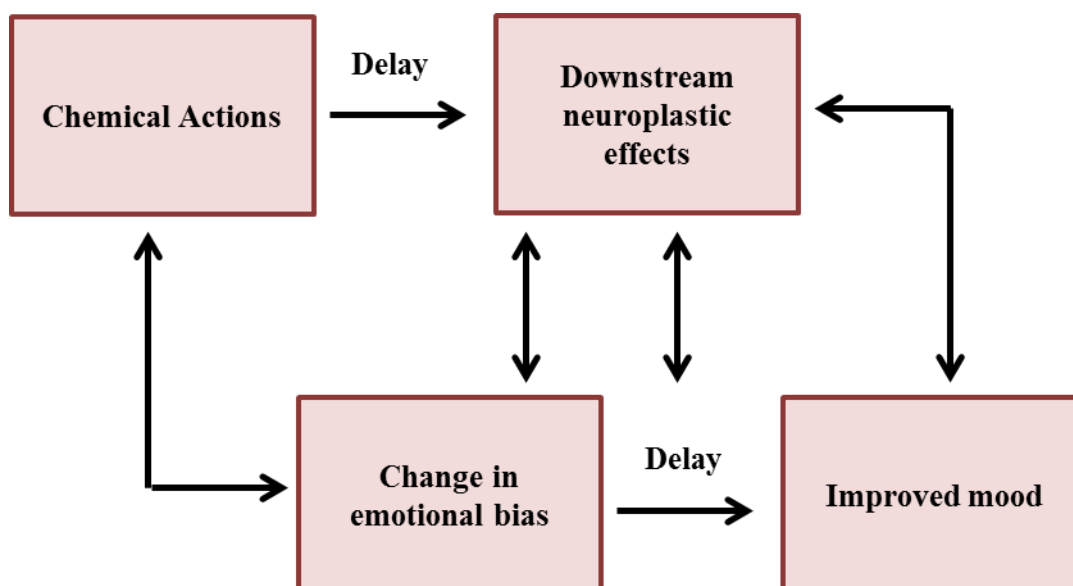


Figure 1.15. The cognitive neuropsychological theory of antidepressant drug action. Taken from Harmer et al., (2017) with permission. This approach demonstrates how psychopharmacology, neurobiological, psychological and environmental factors can be integrated in the examination of antidepressants drug action in depression and the delayed clinical effects of antidepressants.

1.6.3 Modulation of reward processing by antidepressants and dopaminergic agents

Thus far, I have outlined a contemporary approach for understanding the delay in antidepressant drug efficacy in depression focused on the normalisation of neurocognitive mechanisms of negative emotional processing. As reviewed in Sections 1.1.3.1 and 1.5, reward and penalty processing are other important

mechanisms in depression and may be optimal treatment targets. However, there have been comparatively fewer studies in humans investigating how pharmacological agents with antidepressant properties modify reward systems to date. In the next section, I discuss the current evidence for a normalisation response in reward and penalty processing (in healthy and depressed samples) with various antidepressant medication classes used to treat unipolar and bipolar depression. Given the central role of dopamine in the brain's reward circuit and reward processing (discussed in Section 1.3 and 1.4), I also review a larger evidence base on dopaminergic modulation of reward and penalty processing in healthy and depressed sample populations.

A literature search (see Appendix A for search terms and strategy) yielded a total of 44 studies investigating reward and penalty modulation by a variety of antidepressant drug classes used to treat depression (Bauer et al., 2007; Cleare et al., 2015). These are illustrated in Figure 1.16 and included: selective serotonin reuptake inhibitors (SSRIs) (citalopram, escitalopram, paroxetine, fluoxetine) (n=11); serotonin and noradrenaline reuptake inhibitors (SNRIs) (duloxetine) (n=1); selective noradrenaline reuptake inhibitors (NRIs) (reboxetine) (n=1); tricyclic antidepressants (TCAs) (imipramine) (n=1); dopamine and noradrenaline reuptake inhibitor (DNRI) (bupropion) (n=4); dopamine reuptake inhibitors (amphetamines, methylphenidate, modafinil) (n=20); and dopamine antagonists (olanzapine, amisulpride) (n=6). In addition to these seven antidepressant drug classes, we examined modulation of reward and penalty processing by dopamine challenges. This literature review yielded a total of 52 studies across the following drug classes: dopamine antagonists (haloperidol, sulpiride) (n=14); dopamine precursor depletion (acute phenylalanine and tyrosine depletion, alpha-methyl-para-tyrosine) (n=10); dopamine synthesis enhancement (L-DOPA) (n=13); dopamine agonists (bromocriptine, cabergoline, pramipexole) (n=14); dopamine metabolism inhibitors (tolcapone) (n=1). As shown in Table 1.8, these studies varied by (i) sample type (healthy control sample only, both HC and depressed patient groups); (ii) study design (within-subjects cross-over, between-subjects parallel design); (iii) medication duration (acute, prolonged); (iv) administration (oral, intravenous); (v) task (active and passive task paradigms aimed at probing reward and penalty processing, such as the monetary incentive delay (MID) task and pleasant/aversive visual cues, respectively).

Table 1.8. Overview of the pharmacological studies examining the modulation of reward and penalty processing by (A) different medication classes used to treat MDD (Selective serotonin reuptake inhibitors (SSRIs) (citalopram, escitalopram, paroxetine, fluoxetine); Serotonin and noradrenaline reuptake inhibitors (SNRIs) (duloxetine); Selective noradrenaline reuptake inhibitors (NRIs) (reboxetine); Tricyclic antidepressants (TCAs) (imipramine); Dopamine and noradrenaline reuptake inhibitor (DNRI) (bupropion); Dopamine reuptake inhibitor (amphetamines, methylphenidate, modafinil); and Dopamine antagonists (quetiapine, aripiprazole, risperidone, olanzapine, amisulpride) and (B) dopamine challenges (Dopamine antagonists (haloperidol, sulpiride); Dopamine precursor depletion (acute phenylalanine and tyrosine depletion, alpha-methyl-para-tyrosine); Dopamine synthesis enhancement (L-DOPA); Dopamine agonists (bromocriptine, cabergoline, pramipexole); Dopamine metabolism inhibitors (tolcapone). *time interval between drug administration and experimental session. **significant after correction for multiple comparisons with FWE, FDR, Bonferroni or permutations. Relative to placebo unless otherwise specified. ***indicates drugs used in the treatment of MDD. N.s = non significant.

Drug	Reference	Sample type and size	Study design	Route	Dose	Acute/chronic	Time after drug*	Behavioral paradigm	Behavioral effects	BOLD**	EEG MEG
Selective Serotonin reuptake Inhibitor (SSRI)											
Citalopram* **	Macoveanu (2013b)	Healthy control sample (n=24)	Within-subject (counter-balanced) single-blind	IV	20 mg	Acute	2h and maintained during (8mg/h IV)	Active: card gambling task (different risk levels, reward and penalty magnitudes)	N.s change in risk-choice preference, RTs	↓dmPFC to negative outcomes. ↑ amygdala to negative outcomes.	-
	McCabe (2010)	Healthy control sample (n=45)	Placebo-controlled, between-subjects, double-blind	Oral	20 mg	Chronic	7 days	Passive: Visual and taste - reward (chocolate), aversive (moldy strawberries)	N.s change in subjective ratings of pleasantness, intensity, and wanting.	↓VS and vmOFC to rewarding stimuli. ↓ IOFC to aversive stimuli.	-
	Del-Ben (2005)	Healthy male control sample (n=12)	Within-subject (counter-balanced) single-blind	IV	7.5 mg	Acute	12.5minute	Active: Loss/no loss task	N.s change in RT and accuracy	↑ insula and ↓ OFC to No-loss Vs. Loss	-

	Scholl (2017)	Healthy control sample (n=29)	Placebo-controlled, between-subjects, double-blind	Oral	20 mg	Chronic	14 days	Active: Learning task: appetitive (money) and aversive (effort)	↑ reward learning.	↑vmPFC, mid cingulate cortex and parietal cortex RPE signals and ↑dACC(more negative) effort-related PE signals.	-
	Kumar (2008)	Healthy control and long-term medicated un-responsive MDD sample (SSRIs, SNRIs, TCAs, mood stabilisers) (HC: n=15 MDD: n=15)	Within-subject (counter-balanced) (for HC group)	Oral	HC group: 20mg	Chronic	3 days	Active: Pavlovian reward-learning task (pictures predict water)	N.s change in perceived pleasantness of water or accuracy.	↓ rostral ACC, retrosplenial cortex, hippocampus in medicated HC (relative to unmedicated state).	-
	Macoveanu (2014)	Healthy first-degree relatives of patients with MDD (rMD+) (n=24)	Placebo-controlled, within-subjects, cross-over (counter-balanced) double-blind	Oral	10mg	Chronic	4 weeks	Active: card gambling task (different risk levels, reward and penalty magnitudes)	N.s change in risk-choice preference	↓ OFC to low-risk negative outcomes. ↑ hippocampus to high-risk positive outcomes.	-
	Stoy (2012)	Healthy control and unmedicated MDD sample (HC: n= 15; MDD: n =15)	Within-subject (counter-balanced) single-blind	Oral	MDD group: 5mg (add 5mg every 3 days until therapeutic dose reached, mean: 17.7mg, range 10-30mg)	Chronic	6 weeks	Active: MID task (different reward and penalty magnitudes)	↑ self-reported effort during incentive trials. N.s change in RT.	↑VS during penalty anticipation. N.s for reward anticipation	-

Escitalopram

Paroxetine** *	Abler (2011) (2012)	Healthy male control sample (n=18)	Placebo- controlled, within-subjects, cross-over (counter- balanced) double-blind	Oral	20 mg	Chronic	7 days	Passive: Visual erotic stimuli	↓ subjective sexual arousal	↓ NAccc, sub- and pregenual ACC, posterior MCC (relative to bupropion and placebo)	-
	Marutani (2011)	Healthy control sample (n=17)	Placebo- controlled, withi n-subject (counter- balanced) single-blind	Oral	20 mg	Acute	5-5.5h	Active: MID task (different reward magnitudes)	N.s change in RT or accuracy for all trial types.	↓ globus pallidus, dlPFC, insula and putamen to fast RT reward trials.	-
	Graf (2016)	Healthy male control sample (n=17)	Placebo- controlled, within-subjects, cross-over (counter- balanced) double-blind	Oral	20 mg	Chronic	7 days	Active: MID task (different reward magnitudes)	N.s.change in accuracy and RTs	↑ NAccc reward- related PE. n.s for Reward anticipation and outcome	-
Fluoxetine** *	Macoveanu (2014)	Healthy male control sample (n=29)	Placebo- controlled, between- subjects, double-blind	Oral	40 mg	Chronic	3 weeks	Active: card gambling task (different risk levels, reward and penalty magnitudes)	N.s change in risk- choice preference	↓OFC during choice phase. ↓ midbrain (including raphe nuclei) to reward outcomes. N.s effect on negative outcomes	-
Tricyclic Antidepressants											
Imipramine** **	Wichers (2009)	Healthy control sample and unmedicated MDD sample (HC: n=22; MDD: n=83)	Placebo- controlled, between- subjects, double-blind	Oral	MDD group: 200mg (starting dose of 50mg/day increased to 200mg)	Chronic	6 weeks	Experience Sampling Procedure: Daily life activity appraisal: stress and reward	↓ stress sensitivity and ↑ reward experience (positive affect reactivity to negatively	-	-

					over the first week)				appraised activities). ↑ reward experience, not ↓ stress sensitivity discriminated between responders versus non-responders.	
Nor-adrenaline Reuptake Inhibitors (NRI)										
Reboxetine** *	McCabe (2010)	Healthy control sample (n=15)	Placebo-controlled, between-subjects, double-blind	Oral	20 mg	Chronic	7 days	Passive: Visual and taste - reward (chocolate), aversive (moldy strawberries)	N.s change in subjective ratings of pleasantness, intensity, and wanting.	N.s VS change. ↑ medial PFC to reward. ↓ IOFC to aversive stimuli.
Serotonin and noradrenaline reuptake inhibitor (SNRI)										
Duloxetine** *	Ossewaarde (2011)	Healthy control sample (n=26)	Placebo-controlled, within-subjects, double-blind	Oral	60 mg	Chronic	14 days	Active: MID task (one level of reward only)	N.s change in RT	↑ VS during reward anticipation. Correlated with duloxetine plasma levels.
Dopamine and noradrenaline reuptake inhibitor (DNRI)										
Bupropion** *	Abler (2011) (2012)	Healthy male control sample (n=18)	Placebo-controlled, within-subjects, double-blind	Oral	150 mg	Chronic	7 days	Passive: Visual erotic stimuli	N.s change in subjective ratings of sexual arousal	↑ parahippocampus, amygdala, thalamus, FG, posterior MCC
	Dean (2016)	Healthy control sample (n=17)	Placebo-controlled, within-subjects, double-blind	Oral	150 mg	Chronic	7 days	Active: Visual and taste - reward (chocolate),	N.s. change in subjective ratings of stimuli. N.s	↑ vmPFC to reward and aversive stimuli, ↑ vmPFC and ACC to reward

	Walsh (2017)	Healthy control and unmedicated MDD sample (HC: n=42; MDD: n=46)	Within-subjects	Oral	MDD group: 150mg (once daily 7-10 days; 150mg twice daily for 5 weeks)	week 0, week 2, week 6	week 0, week 2, week 6	Active: Probabilistic Instrumental Learning task	aversive (moldy drink). (Anticipation, effort and consummatory phase)	change in RT.	during anticipation. ↑vmPFC, striatum, ACC and motor cortex during effort phase. ↑medial OFC to reward and aversive stimuli, ↓caudate to reward, ↑amygdala and VS to aversive stimuli, during consummatory phase.	-
										Week 0-2: ↓response bias for high-probability wins in MDD. Normalised by week 6 in MDD to resemble HC.		-
	Dopamine antagonists											
	Graf (2015)	Healthy-control sample (n=20)	Placebo-controlled, within-subjects, double-blind	Oral	200 mg	Acute	Under subchronic treatment: 2h after last dose	Erotic stimulus processing		N.s.	N.s.	-
Amisulpride* **	Kahnt (2015)	Healthy-control sample (n=51)	Placebo-controlled, between-subjects, double-blind	Oral	400 mg	Acute	1.5h	Simple reward prediction task		N.s.	↑OFC pattern distinction between reward and no reward, ↑OFC for content-specific representations	-

	Jocham (2011)	Healthy-control sample (n=18)	Placebo-controlled, between-subjects, double-blind	Oral	200 mg	Acute	2.5 h	Reinforcement learning and choice task.	N.s. on initial reinforcement learning, but ↑ ability to select the better of 2 high rewards in a later phase that involved novel choice situations	↑ striatum during prediction errors, ↑ vmPFC during tracking of learned value in transfer phase	-
	Jocham (2014)	Healthy-control sample (n=18)	Placebo-controlled, between-subjects, double-blind	Oral	400 mg	Acute	2.5 h	Reinforcement learning	↓ both approach and avoidance learning	↓ both appetitive and aversive striatal PEs	-
Aripiprazole ***	Bolstad (2015)	Healthy control sample (n=54)	placebo-controlled, between-subjects	Oral	5 or 10 mg	Acute	4.5h	Active: Aversive conditioning task (aversive and neutral events as sounds)	N.s change in aversive versus neutral event avoidance (relative to placebo). ↑ avoidance success rate relative to haloperidol	N.s difference in VS activity relative to placebo and haloperidol. N.s trend aripiprazole group intermediate VS activity to placebo and haloperidol groups.	-
Olanzapine** *	Abler (2007)	Healthy-control sample (n=8)	Placebo-controlled, within-subjects, double-blind	Oral	5 mg	Acute	5 h	Delayed incentive paradigm	↓ reaction time acceleration in trials with higher rewards	↓ ventral striatum, ACC and IFC during reward-related activation	-

	Hawkins (in press, 2018)	Healthy- control sample (n=17)	Placebo- controlled, within-subjects (counterbalance d), double-blind	Oral	7.5mg	Acute	5h	MID	-	<p>↓ caudate activity to reward anticipation (after controlling for neuro-vascular effects).</p> <p>↑ putamen activity (but not after controlling for CBF)</p>	-
Haloperidol	Frank & O'Reilly (2006)	Healthy- control sample (n=28)	Placebo- controlled, within-subjects (counterbalance d), double-blind	Oral	2 mg	Acute	Not clearly described	Go-No go task / Reversal Learning	↑ Go learning from positive reinforce- ment.	-	-
	Hawkins (in press, 2018)	Healthy- control sample (n=17)	Placebo- controlled, within-subjects (counterbalance d), double-blind	Oral	3mg	Acute	5h	MID	-	N.s change during reward anticipation or outcome	-
	Zack (2007)	Healthy- control sample (n=18)	Placebo- controlled, within-subjects (counterbalance d), double-blind	Oral	3 mg	Acute	2.75 h	Gambling- related reward effects	↑ gambling- induced elevation in BP. N.s. on subjective effects.	-	-
	Pleger (2009)	Healthy- control sample (n=30)	Placebo- controlled, between- subjects, double-blind	Oral	1 mg	Acute	4h	Somatosensor y Decision- Making	↓ correct somatosenso ry judgments	↓ ventral striatum, OFC, primary sensorymotor cortex	-
	Oei (2012)	Healthy- control sample (n=55)	Placebo- controlled, between- subjects, double-blind	Oral	3 mg	Acute	3h	Backward- masking task with subliminally presented sexual stimuli	N.s.	↓ NAcc and dorsal ACC	-

	Pine (2010)	Healthy-control sample (n=40)	Placebo-controlled, within-subjects, double-blind	Oral	1.5 mg	Acute	0.5h	Intertemporal choice task	N.s.	N.s.	-
	Bolstad (2015)	Healthy control sample (n=54)	placebo-controlled, between-subjects	Oral	2 or 3 mg	Acute	4.5h	Active: Aversive conditioning task (aversive and neutral events as sounds)	<p>↓ in aversive versus neutral event avoidance (relative to placebo). ↓ avoidance success rate relative to aripiprazole.</p>	<p>↓ R VS (aversive>neutral) relative to placebo. Positive correlation with behavioural data.</p>	-
	Pessiglione (2006)	Healthy-control sample (n=39)	Placebo-controlled, between-subjects, double-blind	Oral	1 mg	Acute	3h	Go-No go task	<p>↓ frequency of high probability gain choices (relatively to L-DOPA); N.s on loss choices Disrupted the correlation between bet size and pay-off observed during placebo</p>	<p>↓ striatal positive and negative responses (relatively to L-DOPA) in gain condition; N.s. in loss condition</p>	-
	Tremblay (2010)	Healthy-control sample (n=18)	Placebo-controlled,	Oral	3 mg	Acute	2.75h	Commercial slot machine		-	-
Sulpiride	Dodds (2008)	Healthy-control sample (n=20)	Placebo-controlled, within-subjects, double-blind	Oral	400 mg	Acute	2h	Reversal Learning task	N.s.	N.s.	-

Sulpiride	Eisenegger (2014)	Healthy-control sample (n=78)	Placebo-controlled, between-subjects, double-blind	Oral	800 mg	Acute	3h	Reinforcement learning	↓ reward-representing stimuli choice; N.s. on learning or avoidance performance	-	-
	McCabe (2011)	Healthy-control sample (n=30)	Placebo-controlled, between-subjects, double-blind	Oral	400 mg	Acute	4h	Rewarding (taste or sight of chocolate) and aversive stimuli (sight of mouldy strawberries or unpleasant strawberry taste)	N.s.	↓ striatum (ventral) and ACC to chocolate stimuli; ↓ lateral OFC and insula to taste and sight of aversive stimuli	-
	van der Schaaf (2013)	Healthy-control sample (n=28)	Placebo-controlled, within-subjects (counterbalanced), double-blind	Oral	400 mg	Acute	2h 15min	Reversal Learning task	↑ reward relative to punishment-based reversal learning after (compared with bromocriptine)	↑ striatum during rewards and punishments.	-
	Medic (2014)	Healthy-control sample (n=47)	Placebo-controlled, between-subjects, double-blind	Oral	400 mg	Acute	2,5h	Value-based decision-making for food items during fasting	N.s.	↓ inferior parietal gyrus/intraparietal sulcus in response to late stage valuation value	-
	Jannsen (2015)	Healthy control sample (n=22)	placebo-controlled, within-subject (counter-balanced), double-blind	Oral	400mg	Acute	3.5h	Reversal Learning Task (reward and punishment)	↓ reward versus punishment-based reversal learning	-	-

	Diederer (2017)	Healthy control sample (n=63)	placebo- controlled, between- subject, double- blind		600mg	Acute	2.5h	Active: Predict magnitude of upcoming rewards (rewards drawn from small, medium or large variability)	<p>(shift away from reward learning). ↓performance (increased error rate). N.s correlations with depression/a nxiety. N.s correlation with WM capacity (proxy for striatal DA synthesis capacity).</p> <p>↓ performance (error)</p>	<p>↓ midbrain for adaptive PE coding and ↓VS for positive PEs relative to placebo.</p>	-
Dopamine reuptake Inhibitors											
Amphetamin e***	O'Daly (2014)	Healthy- control sample (n=22)	Placebo- controlled, between- subjects, double-blind	Oral	20 mg	Acute	2h	Reward Gambling Task	N.s.	<p>↓ dorsal striatum during decision making; ↑ ventromedial caudate during reward anticipation; ↓ amygdala during reward outcomes</p>	-

Amphetamin e***	Childs (2013)	Healthy- control sample (n=34)	Placebo- controlled, within-subject, double-blind	Oral	20 mg	Acute	NA	Conditioning place test	↑ preference for a place associated with drug intake ↓ Stop reaction times in highest dose ↓ number of commission errors and ↑ correct responses ↓ Delay discounting in the higher dose N.s. for gratification	-	-
	Wit (2002)	Healthy- control sample (n=36)	Placebo- controlled, within-subject, double-blind	Oral	10 and 20 mg	Acute	1.5h	Stop task Go/No-go task Delay discounting Delay of gratification	↑ number of break point and capsules in performance session both doses); ↑ subjecti ve ratings of "liking the drug"	-	-
	Rush (2001)	Healthy- control sample (n=8)	Placebo- controlled, within-subject, double-blind	Oral	10 and 20 mg	Acute	NA	Modified Progressive- ratio procedure	↑ (2-fold) in mean 'Addition Research Centre Inventory'	↓ vIPFC, SMC, PMC, caudate and putamen in MDD versus HC at peak drug. N.s pre-drug difference between	-
Dextro- amphetmaine ***	Tremblay (2005)	Healthy control and unmedicated MDD sample (HC: n=12; MDD: n=12)	within-subjects (pre-drug/post- drug), single- blind	Oral	30mg	Acute	90minutes	Active: International Affective Picture System (rating postive,			-

								negative and neutral images)	composite score in MDD versus HC (pre-drug to post-drug). N.s change in pleasantness ratings.	MDD and HC.	
Methamphetamine	Mayo (2013)	Healthy-control sample (n=87)	Placebo-controlled, within-subject, double-blind	Oral	20 mg	Acute	NA	Conditioning place test	↑ preference for a context associated with drug intake - unrelated to subjective drug effects	-	-
	van der Schaaf (2013)	Healthy-control sample (n=19)	Placebo-controlled, within-subjects (counterbalanced), double-blind	Oral	20 mg	Acute	165 min after drug intake	Reversal Learning task	↑ reward (vs punishment) learning in high-working memory subjects, the opposite in low-working memory subjects	-	-
	Costa (2012)	Healthy-control sample (n=54)	Placebo-controlled, within-subjects, double-blind	Oral	40 mg	Acute	1h	Go-No go task	N.s.	↑ putamen during unsuccessful go/no-go inhibition trials; N.s. during successful trials	-

Methylpheni date***	Clatworthy (2009)	Healthy- control sample (n=10)	Placebo- controlled, within-subjects, double-blind	Oral	60 mg	Acute	1h	Reversal Learning task	N.s.	-	-
	Dodds (2008)	Healthy- control sample (n=20)	Placebo- controlled, within-subjects, double-blind	Oral	60 mg	Acute	1,5h/2h	Reversal Learning task	N.s.	↓ ventral striatum during response switching after negative feedback; ↓ ACC and VLPFC during correct responses;	-
	Volkow (2014)	Healthy- control sample (n=19)	Placebo- controlled, between- subjects, double-blind	IV	0,5 mg/kg	Acute	2h	Appraisal of a cocaine cue- video versus a neutral-video	↑ self reports of "high"	-	-
	Volkow (2002)	Healthy- control sample (n=10)	Placebo- controlled, within-subjects, double-blind	Oral	20 mg	Acute	0,75h	Nonhedonic food stimulation	↑ self- reports of "hunger" and "desire for food"	-	-
	Volkow (2004)	Healthy- control sample (n=16)	Placebo- controlled, within-subjects, double-blind	Oral	20 mg	Acute	1h, 1,5h, 2h	Solving mathematical problems with monetary reinforcement	↑ subjecti ve reports of interest and motivation in maths task ↑ accuracy in reward- congruent, incongruent, and non reward- congruent trials; N.s. in non-reward- incongruent trials	-	-
	Ivanov (2014)	Healthy- control sample (n=16)	Placebo- controlled, within-subjects, double-blind	Oral	0,5 mg/kg	Acute	1h	Anticipation Conflic Reward(ACR) task.	↑ insula and the caudate during response to reward cues	-	-
Methylpheni date***											

Methylpheni date***	Duka (2015)	Healthy- control sample (n=397)	Placebo- controlled, between- subjects, double-blind	Oral	20 mg	Acute	1,5h	Conditioned Reinforcement Task	↑ number of presentations of stimulus associated with reward in subjects carrying protective GABRA2 genotype	-	-
	Rush (2001)	Healthy- control sample (n=8)	Placebo- controlled, within-subject, double-blind	Oral	20 and 40 mg	Acute	NA	Modified Progressive- ratio procedure	↑number of breaking points at high dose	-	-
	Marquand (2011)	Healthy- control sample (n=15)	Placebo- controlled, within-subjects, double-blind	Oral	30 mg	Acute	135 min	Rewarded Working Memory task	N.s. Non-rewarded trials: MPH produced a similar activation pattern to reward; Rewarded trials: opposite effect to reward, attenuating WM networks and enhancing task- related deactivations in regions of the DMN; in the delay component of rewarded trials, MPH produced greater activity in WM networks; during encoding, MPH mimics reward pattern	-	-

	Funayama (2014)	Healthy-control sample (n=20)	Placebo-controlled, within-subjects, double-blind	Oral	200 mg	Acute	2. 5h	Monetary incentive delay task	<p>↑ Visual Analogue Score effort scores for highest gain or loss cues</p> <p>N.s.</p>	-
	Evers (2016)	Healthy control sample (n=20)	placebo-controlled, within-subjects (counter-balanced), double-blind	Oral	40mg	Acute	108 minutes	Active: Gambling task (Pavlovian, choice has no implication for the outcome)	<p>↑ response vigor (decreased RTs)</p> <p>↑ VS for reward expectancy. ↓ VS to gain and loss outcome.</p>	-
	Stoops (2004)	Healthy-control sample (n=7)	Placebo-controlled, within-subjects, double-blind	Oral	10, 20 and 40 mg	Acute	NA	Modified progressive-ratio procedure	<p>↑ number of break point and capsules in performance session (dose-dependent);</p> <p>↑ subjective rating of “liking the drug”;</p>	-
Modafinil***	Stoops (2005)	Healthy-control sample (n=6)	Placebo-controlled, within-subjects, double-blind	Oral	100, 200 and 400 mg	Acute	NA	Modified progressive-ratio procedure	<p>↑ number of break point and capsules in performance session (dose-dependent);</p> <p>↑ subjective rating of “liking the drug”;</p>	-

	Funayama (2014)	Healthy-control sample (n=20)	Placebo-controlled, within-subjects, double-blind	Oral	200 mg	Acute	2.5h	Monetary incentive delay task	↑ Visual Analogue Score effort scores for highest gain or loss cues	N. s	-
Dopamine's precursors depletion											
Acute phenylalanine and tyrosine depletion	Cox (2015)	Healthy-control sample (n=15)	Placebo-controlled, within-subjects (counterbalanced), double-blind	Oral	-	Acute	4h	Probabilistic Selection Task	↑ learning from negative outcome; N.s. from positive feedback	-	-
	Kelm (2013)	Healthy-control sample (n=15)	Placebo-controlled, within-subjects (counterbalanced), double-blind	Oral	-	Acute	5h	Delay-discounting task	↑ impulsive choice ratio among Val homozygotes and ↓ among Met carriers. No main effect.	-	-
	Bjork (2014)	Healthy-control sample (n=16)	Placebo-controlled, within-subjects (counterbalanced), double-blind	Oral	-	Acute	5h	Monetary incentive delay task	N.s.	↓ bilateral NAcc during reward anticipation (correlated with ↓ mood following administration, in left NAcc)	-

Acute phenylalanine and tyrosine depletion	McLean (2004)	Healthy- control sample (n=40)	Placebo- controlled, between- subjects, double-blind	Oral	-	Acute	5h	Neuropsychological assessment	↓ content ment and ↑ apathy; ↑ sad latency bias in affective go/no-go task; ↓ bet increase rate in response to more likely outcomes (decision- making task) ↑punishmen t processing in females but not males	-	-
	Robinson (2010)	Healthy- control sample (n=29)	Placebo- controlled, within-subjects (counterbalance d), double-blind	Oral	-	Acute	4.5 h	Reversal Learning task		-	-
	Frank (2015)	Healthy- control sample (n=36)	Placebo- controlled, within-subjects (counterbalance d), double-blind	Oral	-	Acute	3h	Food-Related Reward	N.s.	↓ striatum and ↑ SFG (both independently of BMI)	-
	Leyton (2007)	Healthy- control sample (n=14)	Placebo- controlled, within-subjects, double-blind	Oral	-	Acute	5.5h	Go/No-go task	↑commission errors in conditions where subjects were rewarded for making correct responses; this effect of prevented by L-DOPA	-	-

	Roiser (2005)	Patients recovered from MDD (n=20)	Placebo- controlled, within-subjects, double-blind	Oral	-	Acute	5h	Neuropsychol ogical assessment. Decion- making gambling game and probabilistic reversal (positive and negative feedback)	N.s change in mood relative to placebo. ↓ risk-taking on decision- making task. N.s change in RT. N.s trend for ↑ negative affective bias in affective go/no go task. N.s change in response to negative or positive feedback in Probabilistic reversal task.	-	-
Alpha- methyl-para- tyrosine	Grob (2012)	Healthy- control sample (n=28)	Placebo- controlled, within-subjects (counterbalance d), double-blind	Oral	40 mg/kg over 22h	Acute	30h after 1st administra tion	Probabilistic reward task	↓ disciminabili ty and reaction times	-	-
	Hasler (2009)	Healthy- control female sample (n=12)	Placebo- controlled, within-subjects (counterbalance d), double-blind	Oral	40 mg/kg body weight p.o., to a maximu m of 4g;	Acute	Over 22 hour	Probabilistic reversal learning task	↑the number of reversal errors for the 80-20 contingency pair;	-	-
								Passive Avoidance Learning task			
								Affective Stroop task	↓ the probability of		

									responding to the S+ stimuli in later blocks (7–10) relative to the earlier blocks;		
									N. s. for the stroop task		
Dopamine synthesis enhancement											
L-DOPA	Eisenegger (2013)	Healthy-control sample (n=200)	Placebo-controlled, between-subjects, double-blind	Oral	300/75 mg L-DOPA / benserazide	Acute	50 min after	Social interaction task	↑ learning in DAT1 VNTR 10-repeat homozygotes), ↓ in 9-repeat carriers subjects	-	-
	Guitart-Masip (2012)	Healthy-control sample (n=52)	Placebo-controlled, between-subjects, double-blind	Oral	150/37.5 mg L-DOPA/ benserazide	Acute	1h	Go-No go task	↑ velocity of go responses	↑ Bilateral putamen, caudate and SN/VTA in Go-to-win trials; N.s. in Go-to-avoid-losing trials;	-
	Beierholm (2013)	Healthy-control sample (n=90)	Placebo-controlled, between-subjects, double-blind	Oral	150/37.5 mg L-DOPA/benserazide	Acute	1h 40 min	Odd-ball discrimination task	↑ the impact of reward rate in response time	-	-

L-DOPA	Chowdury (2013)	Healthy-control sample (n=54)	Placebo-controlled, within-subject, double-blind	Oral	150/37.5 mg L-DOPA/benserazide	Acute	1h	Two-arm bandit task	↑ learning rate and performance in some older adults to the level of young adults	↑NAcc in older people to levels similar to young	-
	Wittmann (2015)	Healthy-control sample (n=28)	Placebo-controlled, between-subjects, double-blind	Oral	100/10 mg L-DOPA/carbidopa	Acute	Alternating reward and punishment	N.s.		↑striatum for all cue types shown in punishment blocks.	-
	Pedroni (2014)	Healthy-control sample (n=197)	Placebo-controlled, within-subjects, double-blind	Oral	300 mg	Acute	1h	Economic bargaining game	↑ selfish behaviour in the absence of punishment threats; N.s. in their presence ↑ risky options chosen in trials involving potential gains but not in those involving potential losses; ↑ happiness resulting from some rewards	-	-
	Rutledge (2015)	Healthy-control sample (n=30)	Placebo-controlled, within-subjects (counterbalanced), double-blind	Oral	150/37.5 mg L-DOPA/benserazide	Acute	1h	Economic decision-making task		-	-

L-DOPA	Apitz (2014)	Healthy-control sample (n=38)	Placebo-controlled, between-subjects, double-blind	Oral	150/37.5 mg L-DOPA/benserazide	Acute	1.5h	Visual cue reward prediction task	N.s.	-	↓ oscillatory power in high and low beta band during both reward anticipation and delivery
	Pleger (2009)	Healthy-control sample (n=30)	Placebo-controlled, between-subjects, double-blind	Oral	100 mg	Acute	1h / 4h	Somatosensory Decision-Making	↑ correct somatosensory judgments	↑ ventral striatum, OFC, primary sensorymotor cortex	-
	Oei (2012)	Healthy-control sample (n=55)	Placebo-controlled, between-subjects, double-blind	Oral	100/25 mg L-DOPA/carbidopa	Acute	1h / 3h	Backward-masking task with subliminally presented sexual stimuli	N.s.	↑ NAcc and dorsal ACC	-
	Pine (2010)	Healthy-control sample (n=40)	Placebo-controlled, within-subjects, double-blind	Oral	150 mg	Acute	0.5 h	Intertemporal choice task	↑ in sooner options chosen	↑ caudate and amygdala;	-
	Pessiglione (2006)	Healthy-control sample (n=39)	Placebo-controlled, between-subjects, double-blind	Oral	100/25 mg L-DOPA/benserazide	Acute	1h	Go-No go task	↑ frequency of high probability gain choices; n.s on loss choices (compared to haloperidol)	↑ striatal and insular positive and negative prediction errors (relatively to haloperidol) in gain condition; N.s. in loss condition	-
	Weis (2012)	Healthy-control sample (n=66)	Placebo-controlled, between-subjects, double-blind	Oral	100/25 mg L-DOPA/benserazide	Acute	0.5 h	Appetitive instrumental conditioning paradigm	N.s.	↑ auditory cortex, left Broca's area and anterior cingulate cortex/left superior medial gyrus	-

Dopamine agonists											
Bromocriptine	Cools (2009)	Healthy-control sample (n=11)	Placebo-controlled, within-subjects, double-blind	Oral	1.25 mg	Acute	3.5h	Reversal Learning task	↑ reward-based and ↓ punishment-based reversal learning in low baseline dopamine synthesis capacity subjects; the opposite effects in high capacity subjects.	-	-
	Kirsch (2006)	Healthy-control sample (n=24)	Placebo-controlled, within-subjects, double-blind	Oral	1.5 mg	Acute	2h	Monetary reward condition; Punishment avoidance condition;	↑ reward-anticipation performance in DRD2 Taq1 A1 carriers	↑ NAcc only in A1 carriers	-
	Medic (2014)	Healthy-control sample (n=47)	Placebo-controlled, between-subjects, double-blind	Oral	1.25 mg	Acute	2.5h	Value-based decision-making for food items during fasting	N.s.	↑ inferior parietal gyrus/intraparietal sulcus in response to value	-
	van der Schaaf (2013)	Healthy-control sample (n=28)	Placebo-controlled, within-subjects (counterbalanced), double-blind	Oral	1.25 mg	Acute	2h 45 min	Reversal Learning task	↑ reward relative to punishment-based reversal learning (compared to sulpiride)	N.s.	-

	Diederer (2017)	Healthy control sample (n=63)	Placebo-controlled, between-subject, double-blind	Oral	2.5 mg	Acute	2.5h	Active: Predict magnitude of upcoming rewards (rewards drawn from small, medium or large variability)	N.s change in performance (error)	-	-
Cabergoline	Cohen (2007)	Healthy-control sample (n=23)	Placebo-controlled, within-subjects (counterbalance d), double-blind	Oral	1.5 mg	Acute	1.5 h	Reversal Learning task	↑ learning rate in Taq1A DRD2 A1+subjects and ↓ in A1- ↑ aversive value of punishment outcomes following conflict ↓ Go learning from positive reinforcement; ↑ bias toward overall Go responding.	↑ medial OFC, CC and striatum in A1+ vs. A1- genotypes; ↓ frontostriatal connectivity in A1+ vs. A-.	-
	Cavanagh (2014)	Healthy-control sample (n=30)	Placebo-controlled, within-subjects (counterbalance d), double-blind	Oral	1.25 mg	Acute	2h 22 min (average)	Conflict in a reinforcement learning task		-	N.s.
	Frank & O'Reilly (2006)	Healthy-control sample (n=28)	Placebo-controlled, within-subjects (counterbalance d), double-blind	Oral	1.25 mg	Acute	Not described	Go-No go task / Reversal Learning		-	-
	McCabe (2013)	Healthy-control sample (n=16)	Placebo-controlled, within-subjects (counterbalance d), double-blind	Oral	0.25 mg	Acute	2h	Passive receipt of rewarding, aversive sight and taste stimuli	N.s.	↓ vmPFC, the OFC, striatum, thalamus and dACC during chocolate stimuli; ↓ dACC during aversive stimuli	-

Pramipexole	Ye (2011)	Healthy-control sample (n=16)	Placebo-controlled, within-subjects, double-blind	Oral	0.5 mg	Acute	2h	Monetary Incentive Delay Task	N.s	During the anticipation of monetary rewards: ↑NAcc; ↑ the interaction between the NAcc and the anterior insula; ↓ the interaction between the NAcc and the prefrontal cortex. ↓ rostral basal ganglia (globus pallidus and ventral striatum) and midbrain, following unexpected high gains	-
	Riba (2008)	Healthy-control sample (n=50)	Placebo-controlled, within-subjects (counterbalanced), double-blind	Oral	0.5 mg	Acute	2h	Lottery task	↑ riskier choices following unexpected high wins ↓ response bias toward the most frequently rewarded stimulus; ↓ reaction time and motor speed; ↑ negative affect perception	-	
	Pizagalli (2008)	Healthy-control sample (n=32)	Placebo-controlled, within-subjects (counterbalanced), double-blind	Oral	0.5 mg	Acute	2h	Probabilistic reward task		-	
	Jocham (2011)	Healthy-control sample (n=18)	Placebo-controlled, between-subjects, double-blind	Oral	0.5 mg	Acute	2.5 h	Reinforcement learning and choice task.	Not reported (nonspecific effects)	Not reported (nonspecific effects)	-

	Santesso (2009)	Healthy- control sample (n=32)	Placebo- controlled, within-subjects (counterbalance d), double-blind	Oral	0.5 mg	Acute	2h	Probabilistic reward task	Reported in Pizagalli (2008)	-	↑FRN to probabilistic rewards and decreased activation in dorsal AC regions previously implicated in integrating reinforcement history over time
Dopamine metabolism inhibitors											
Tolcapone	Sáez (2015)	Healthy- control sample (n=35)	Placebo- controlled, within-subjects (counterbalance d), double-blind	Oral	200 mg	Acute	1,5h	Dictator game	↑ egalitarian tendencies; N.s. on the extent to which individuals directly value the material payoffs of others	-	-

1.6.3.1 ***Selective serotonin reuptake inhibitors (SSRIs), serotonin and noradrenaline reuptake inhibitors (SNRIs), selective noradrenaline reuptake inhibitors (NRIs)***

The normalisation of reward-task related processing by antidepressant treatment may have a different temporal response when compared to emotion processing mechanisms. As described in Section 1.6.2.1, several studies show a normalisation of emotional bias with seven day and even acute treatment with SSRIs and noradrenaline reuptake inhibitors (Harmer et al., 2003a; Harmer et al., 2009c; Harmer et al., 2004). In contrast, antidepressants seem to exacerbate reward deficits early in treatment (Kumar et al., 2008; Marutani et al., 2011; McCabe et al., 2010) prior to normalisation following longer-term (two-six week) treatment (Scholl et al., 2017; Stoy et al., 2012a; Walsh et al., 2017). For example, acute dose and seven day treatment with SSRI paroxetine *diminishes* brain activity induced by motivation in healthy subjects in the globus pallidus, insula, putamen, ACC and dorsolateral prefrontal cortex (Abler et al., 2012; Abler et al., 2011; Marutani et al., 2011) and hedonic signals in the NAcc (Graf et al., 2016). Three day treatment with SSRI citalopram in healthy controls reduces reward-related prediction error signalling in the ACC and hippocampus relative to an un-medicated state (Kumar et al., 2008). Seven day treatment with SSRI citalopram in healthy controls *reduces* activation for rewarding and aversive stimuli (in the VS and ventromedial OFC to rewarding stimuli (chocolate) and in the lateral OFC for aversive stimuli) (McCabe et al., 2010). In a similar fashion, McCabe and Mishor (2011) reported reduced connectivity at rest between key regions of the reward network (striatal–orbitofrontal cortex connectivity) in healthy volunteers following 7-day reboxetine (selective noradrenergic reuptake inhibitor, NRI) treatment.

In contrast, prolonged, two week administration of SSRI citalopram *increases* neural responses to reward anticipation (Stoy et al., 2012a) and neural PE signals during reward and effort learning in VMPFC and ACC; and concomitantly improves behavioural measures of reward learning (Scholl et al., 2017; Stoy et al., 2012a). Similarly, two week treatment with serotonin and noradrenaline reuptake inhibitor (SNRI) duloxetine enhances VS responses to incentive cues in the MID task (Ossewaarde et al., 2011). Moreover, improved positive affect in depressed patients

after 2 months anti-depressant medication treatment (citalopram) is related to patients' ability to sustain activity in prefrontal-nucleus accumbens circuitry (Heller et al., 2013). SSRI, NRI and SNRI medication thus seems to enhance neural and behavioural signals of reward only after a prolonged period (2+ weeks), and following an initial decrease in these signals.

However, there are exceptions to this pattern. SSRI fluoxetine has shown to attenuate neural responses during risky decision making and reward outcome in healthy volunteers even after three week intervention (Macoveanu et al., 2014). As there is evidence for different trajectories in reward-related antidepressant response for healthy and depressed subjects (e.g. Walsh et al., 2017), it will be important to replicate this in a sample including both groups. Indeed, without similar studies in patients, extrapolating to the clinical domain needs to be done with caution. This is because patient and control groups will most likely be starting from different baselines (both in terms of aberrant disease processes and evidence that long-term treatment changes the dynamics of the neurotransmitter systems (Goto and Grace, 2007)), which would likely influence BOLD signal. Finally, it is important to note that reward-related cortico-striatal connectivity predicts symptom change. A more normative pattern of ACC-caudate connectivity during reward and penalty processing prior to 12 week escitalopram treatment is associated with greater improvement in symptoms 12 weeks later (Admon et al., 2015a).

Moreover, it is logical to consider how antidepressants with different mechanisms of action at the receptor level (serotonergic, dopaminergic, noradrenergic) affect the behavioural and neural correlates of reward processing at different timescales. Indeed, it has been suggested that antidepressants with an effect on the dopamine reward system may be more efficacious at improving reward-related deficits and suited to treat apathy and anhedonia (Argyropoulos and Nutt, 2013; Nutt et al., 2007).

1.6.3.2 *Dopamine Reuptake Inhibitors: Bupropion, amphetamines, methylphenidate, modafinil*

Dopamine reuptake inhibitors increase dopamine transmission by blocking the action of the dopamine transporter (DAT) during dopamine reuptake in the synapse (Melega et al., 1995). When dopamine is blocked from re-entering the pre-synaptic neuron, the

results is an increased extra-cellular concentration of dopamine which is available for transmission to the post-synapse (Oswald et al., 2015).

Bupropion is one of the few antidepressants that prevent the reuptake of dopamine (in addition to noradrenaline) (i.e. dopamine and noradrenaline reuptake inhibitor, DNRI) (Dwoskin et al., 2006; Stahl et al., 2004). It shows a similar temporal profile to SSRIs in terms of normalisation of behavioural responses to reward. Compared to placebo, a single dose of bupropion had unexpected detrimental effects on reward processing in healthy volunteers (Walsh et al., submitted). Similarly, bupropion exacerbated reward deficits in depressed individuals, with a significant decrease in the likelihood of choosing high-probability wins between baseline and week two. However, by week six, bupropion was found to normalise reward processing to healthy control levels (Walsh et al., 2017). At the neural level, however, bupropion differs to SSRIs in that it increases neural responses to rewards early in treatment. After seven days, bupropion already enhances fronto-striatal responses to erotic images (Abler et al., 2011) and to anticipation, effort and consummation of reward and aversion (Dean et al., 2016). Yet, there were no treatment effects on behavioural and subjective reports of pleasantness, wanting and intensity for positive and aversive stimuli (Dean et al., 2016). This may suggest that increased neural activity to reward and aversion after seven days does not necessarily become the subject of conscious awareness (McCabe et al., 2010).

Although it is not possible to directly compare results for the SSRI and DNRI antidepressant studies, due to differences in passive (McCabe et al., 2010) versus active tasks (Dean et al., 2016) respectively, the results suggest that drugs with different neurotransmitter targets interact with reward and aversion differently. The findings that the neuropsychological effects of bupropion on reward and aversion occur very early, before changes in mood or behaviour, is consistent with the neuropsychological model of antidepressant action (Harmer and Cowen, 2013). However, studies with larger sample sizes and in depressed patients (to avoid ceiling effects), over a longer period of time are required to strengthen these preliminary findings.

Amphetamines, methylphenidate and modafinil are DA reuptake inhibitors that are no longer or less commonly used for the treatment of MDD. Indeed, amphetamine has been associated with increased susceptibility for addictive behaviours, driven by increased concentrations of striatal dopamine (Vaughan and Foster, 2013). Thus, in

reward processing, a number of studies have reported enhanced caudate activation during reward anticipation (O'Daly et al., 2014) and increased place preference (Childs and de Wit, 2013) (however also see Knutson et al., (2004) and discussion below). Recently FDA-approved wakefulness-promoting modafinil (200 mg) was shown to increase the subjective effort score for monetary gains in the MID task (Funayama et al., 2014). A study with metamphetamine (20mg) also found an increase of preference for the context in which the drug was administered, and this was unrelated to subjective drug effects. This suggests that metamphetmaine has specific effects on reward processing without altering general mood, as has been observed for bupropion (Mayo et al., 2013). However, this study was only completed in a healthy control sample. There was only one study completed in depressed individuals with an IAPS task (which consists of rating a set of validated pictures containing neutral, positive, and negative images of humans, animals, and objects) (Tremblay et al., 2005). Dextro-amphetamine lead to MDD subjects having a hypersensitive response to the rewarding effects of dextroamphetamine (two-fold increase) relative to healthy controls (Tremblay et al., 2005).

This is similar to a study in rodents which investigated the ability of drugs that block dopamine transport (DAT), norepinephrine transport (NET), and serotonin transport (SERT) to modulate work output in rats responding on a test of effort-related decision making (a progressive ratio (PR)/chow feeding choice task) (Yohn et al., 2016a; Yohn et al., 2016b). Rats choose between working for a preferred food by lever pressing on a PR schedule versus obtaining a less preferred lab chow that is freely available in the chamber. Acute and repeated administration of DAT inhibitor GBR12909 shifted choice behaviour, increasing measures of PR lever pressing and decreasing chow intake. In contrast, SSRI fluoxetine and noradrenaline inhibitors desipramine and atomoxetine failed to increase lever pressing output, and actually decreased it at higher doses. Moreover, the increased selection of the high effort instrumental activity under the DAT inhibitor was related to elevated extracellular dopamine levels in the NAcc core, whilst fluoxetine, desipramine and atomoxetine decreased extracellular dopamine. The same group also investigated how different classes of antidepressants reverse the effects of tetrabenazine, which produces depressive symptoms in humans and biases effort-based decision making toward low effort/low reward options versus high effort/high reward options (Yohn et al., 2016a). In rats, the effort-related effects

of tetrabenazine were attenuated by DNRI bupropion, whilst SSRI fluoxetine and NRI desipramine failed to reverse the effects of tetrabenazine, with higher doses leading to further behavioural impairments. Thus, medications working on dopamine transmission seem to be effective at increasing choices for high effort/high reward options and are consistent with the hypothesis that drugs that enhance dopamine may be affective in treating anhedonia and depression.

There are however some findings which are counterintuitive to this proposal. The same study that found increased behavioural responses to reward in depressed patients on dextro-amphetamine, also showed negative (rather than increased) neural BOLD responses in the caudate, putamen and prefrontal OFC to rewards (Tremblay et al., 2005). The physiological mechanisms of negative BOLD signals are thought to be induced by reduced cerebral blood flow (i.e. active neuronal inhibition and decreased cortical excitability) (Shmuel et al., 2002; Stefanovic et al., 2004). Interestingly, other studies with methylphenidate (30 mg and 40 mg dose) have also found decreases in the typical effect of reward on brain function during rewarded trials (Dodds et al., 2008; Marquand et al., 2011). This could be explained by the discrimination between rewarded and unrewarded processes being reduced on drug (amphetamine).

Dextroamphetamine and methylphenidate may increase tonic dopamine release to a level that dampens the transient phasic burst firing that encodes reward. This provides a context in which the phasic signals that mark rewarding stimuli are 'drowned' out and do not appreciably change the BOLD signal (Grace, 1991; Grace, 2016). Another speculative explanation for these results is an inverted U-shape effect of dopamine dosing on reward coding. Unfortunately, the pharmacological imaging studies of bupropion administration were only conducted after pro-longed administration. Thus, acute administration of bupropion in conjunction with neuroimaging is required to examine the overlap of findings between bupropion and other drugs within this class of dopamine reuptake inhibitor (DRIs).

In summary, the evidence thus far points to a dissociation in the temporal effects of antidepressants on emotional and reward processing, and also the need to consider how antidepressants with different mechanisms of action at the receptor level (dopaminergic, noradrenergic, serotonergic), may affect the behavioural and neural-correlates of reward processing at different timescales. The evidence suggests that an acute or seven day dose of agents acting on dopamine receptors (e.g. bupropion) is

sufficient to enhance neural signals to reward but not behaviour or learning (Dean et al., 2016; Walsh et al., 2017); whilst SSRIs enhance neural and behavioural signals of reward after a prolonged period (2+ weeks).

As outlined in Section 1.1.5.2, clinical guidelines for the pharmacological treatment of MDD, not only include SSRIs, SNRIs, NRIs and DNRI, but also augmentation or combination treatment with dopamine antagonists when an individual does not respond to first-line treatment. First-line augmentation treatments include quetiapine and aripiprazole, and second-line treatments include risperidone and olanzapine. Therefore, I will now review evidence for the modulation of reward and penalty function by dopamine antagonists. Critically, dopamine antagonists can be split into two categories. First generation or typical antipsychotics are prototypical D₂ antagonists, such as haloperidol, which are not used in MDD treatment. Second generation or atypical antipsychotics, have a broader receptor binding profile, including greater noradrenergic and serotonergic action (e.g. amisulpride, olanzapine, quetiapine, lurasidone) and are used in treatment of depression. In the next section, I present experimental evidence of dopamine antagonist modulation of reward (cognitive and neural) in healthy volunteers and depressed individuals. I discuss limitations and considerations for the interpretations of neuropharmacology research on reward processing.

1.6.3.3 ***Dopamine antagonists: olanzapine, amisulpride, haloperidol, sulpiride***

Dopamine antagonists blocks dopamine receptors by receptor antagonism and therefore interfere with dopamine neurotransmission ((Boissier and Pagny, 1960). There are very few studies investigating the modulation of reward and penalty processing by antidepressant D₂ antagonists (amisulpride n=5, olanzapine n=1, aripiprazole n=1), and the majority of the studies have been completed in typical antipsychotic haloperidol (n=8).

Beginning with D₂ antagonists with antidepressant properties, acute olanzapine administration (5 mg) does not blunt overall VS reward-related activity, but rather equalises the assignment of salience (i.e. reduces activation differences) between high,

low and not-rewarded trials (Abler et al., 2007). Behavioural effects included reduced reaction time acceleration for high rewards. In contrast, one week olanzapine treatment in healthy volunteers increased BOLD response during both anticipation of rewarding tastes and reward receipt in the striatum and ACC. The differences in these results could reflect different doses, length of treatment, or task paradigms, as the experience of a primary reward is clearly different to the indirect reward of money (a secondary reward) in the MID task (Sescousse et al., 2013). Further studies with olanzapine are required as the study by Abler et al., (2007) used a very small sample size ($n=8$) that is less than that needed for reliable group comparison in fMRI (Thirion et al., 2007).

The findings in amisulpride are more robust, due to the greater number of studies and variety of doses used. There seems to be a dissociation in effects on reward for low (<200 mg) versus high (>400 mg) doses of acute amisulpride administration. Kahnt et al., (2015) found that amisulpride at low doses (200 mg) increased OFC pattern distinction between reward and no reward. At the same dose, amisulpride also increased the ability to select the better of two high rewards in a reward learning task and this was accompanied by increased activity in the striatum during prediction errors and the ventromedial PFC during tracking of learnt value (Jocham et al., 2011). Only one study directly examined response to dopamine antagonists in depressed patients, thereby uniting three components: investigating reward and penalty modulation by dopamine antagonists in depression. Admon et al., (2017) showed that a single low dose of the amisulpride (50 mg) normalised reward processing by increasing reward-related striatal activation and corticostriatal connectivity in depressed individuals, without increasing reward learning. These findings suggest that low dose amisulpride predominantly increases reward coding. Moreover, they raise the intriguing possibility that dopamine antagonists—some of which are efficacious antidepressants—may exert their effects via reward signal normalisation. In contrast, at a double dose (400 mg), amisulpride has been shown to decrease both approach and avoidance learning as well as reward- and aversive-related striatal PEs (Jocham et al., 2014).

Therefore, an affinity-based model (also discussed in DA agonists in Section 1.6.3.4), could be applied here to understand the observed association between low dose D_2 antagonist and higher reward coding and between high dose and attenuated reward coding. Specifically, presynaptic D_2 receptors have higher affinity to dopamine than post-synaptic D_2 receptors and would be occupied first at low doses (Frank and

O'Reilly, 2006b). Predominant blockade of presynaptic autoreceptors at low doses could subsequently lead to amplification of dopamine phasic release (also described as a shift of the tonic versus phasic balance towards phasic activity (Dreyer et al., 2010). However, as is the case for dopamine agonists, this dose-dependent rationale of D₂ receptor antagonism on reward processing needs further evidence. There is a clear need for studies using varying doses of dopamine antagonists on phasic versus tonic dopamine firing and release to understand the pre-synaptic actions of dopamine antagonists.

For haloperidol there are mixed findings. Some studies report blunted behavioural and neural correlates of reward processing with 2 mg haloperidol (Pleger et al., 2009a), whereas other studies found no significant effects with similar doses (Oei et al., 2012a; Pine et al., 2010; Zack and Poulos, 2007) or even increased learning from rewards (Frank and O'Reilly, 2006a). A study by Bolstad et al., (2015) specifically examined the effects of acute dose haloperidol (versus aripiprazole and placebo) in an aversive conditioning task with aversive and neutral events presented as sounds. Haloperidol led to a reduction in aversive versus neutral event avoidance (relative to placebo). In other words, participants on haloperidol were not able to actively avoid more aversive trials, whilst these aversive events were successfully avoided in aripiprazole and placebo groups. Accordingly, activity in the VS (aversive>neutral) was reduced in the haloperidol group compared to the placebo group. The aripiprazole group showed task-related activations intermediate of haloperidol and placebo. These findings support the role of dopamine in mediating the motivational salience of environmental stimuli, with haloperidol yielding stronger inhibition of mesolimbic activity than aripiprazole and thus inducing indifference to salient stimuli (Bolstad et al., 2015).

For sulpiride a complex scenario can also be found. Two studies demonstrate reductions in choices for reward-representing stimuli (Eisenegger et al., 2014) and reductions in VS and ACC activation to sight and taste of a primary reward (chocolate) stimuli and of the lateral OFC to aversive stimuli (McCabe et al., 2011) with 400 mg sulpiride. On the contrary, another study using the same dose demonstrated increased reward learning versus penalty-related learning alongside an increase in striatal activation to rewards (van der Schaaf et al., 2014). A review paper of sulpiride suggested inter-individual variability could have driven differences in these studies (Martins et al., 2017).

Taken together, there is a complex picture of the effects of D₂ antagonism on reward and penalty processing. The effects may depend on (i) pre-versus post-synaptic effects, which is related to (ii) drug dose and (iii) inter-individual variation (e.g. genetic variation which affects availability of dopamine receptors and regulators (DAT, COMT) that influence dopamine concentration and signaling. This may be complicated further by the fact that there is little knowledge about the function of phasic DA release in prefrontal regions. Indeed, we must be aware of the regional (frontal versus striatal) differences in dopamine receptor distribution and signaling pathways. For example, the medial PFC receives less dopamine projections (Descarries et al., 1987), has lower tonic levels of DA, and shows less dopamine reuptake transporter relative to the striatum (Bassareo and DiChiara, 1997; Sesack et al., 1998). Thus, these differences are likely to lead to differential effects of the same pharmacological agent at these regions (Hernaus and Mehta, 2016).

Beyond D₂ receptors, it is necessary to acknowledge that some of these drug effects may be mediated by activity at adrenergic and serotonin neurotransmitter systems. Indeed, animal studies suggest that the antidepressant effects of atypical antipsychotics are related to their affinity and activity at 5-HT receptors (Ishibashi et al., 2010; Yatham et al., 2005). Based on electrophysiological recordings and imaging studies in rodents and primates, serotonergic neurons have been shown to directly impact upon reward (and predominantly aversive) processing (Boureau and Dayan, 2011; Cohen et al., 2015; Hayashi et al., 2015; Inaba et al., 2013; Li et al., 2016; Liu et al., 2014). This can also be likened to the effects of SSRI agents to rewards and penalties in Section 1.6.3.1 above (Scholl et al., 2017). Indeed, cortical regions which form part of the incentive-based learning network, such as the OFC and ACC have high densities of 5-HT (1A and 2A) receptors (Boureau and Dayan, 2011; Macoveanu, 2014). Moreover, ascending serotonergic systems show a similar innervation pattern to dopamine and in addition to the overlapping anatomical organisation of these neurotransmitter systems, there is evidence of their interaction at a functional level (Briand et al., 2007). For example, 5-HT_{2C} receptors generally tonically inhibit DA release whilst the majority of 5-HT receptor types (5-HT_{1A}, 5-HT_{2A}, 5-HT₃, 5-HT₄) stimulate dopamine release in the NAcc via excitatory influence on the VTA.

1.6.3.4 ***Dopamine agonists: bromocriptine, cabergoline, pramipexole***

Dopamine agonists activate dopamine receptors and have a relative specificity for dopamine D₂-like receptors (binding to both pre-synaptic autoreceptors and postsynaptic receptor). As with the dopamine antagonist literature, it seems that dopamine agonists have mixed effects on reward processing which may be related to its complex effects on the dopaminergic system that are dependent on dose (high versus low) and a combination of pre- and post-synaptic effects.

It seems that bromocriptine (1.25 mg) increases reward-based learning (Cools et al., 2009). However, this effect was only significant in individuals with low dopamine synthesis capacity, and bromocriptine decreased reward learning in high dopamine synthesis capacity subjects. In a similar way, pramipexole (0.5mg) increased performance and striatal activation to reward anticipation in a MID task, only in a genotype that predisposes an individual to fewer dopamine binding sites (Noble et al., 1991). Again, cabergoline (1.5 mg) increased learning rate and also OFC and striatal activation in this genotype only in a reversal learning task (Cohen et al., 2007). There may be two possible explanations for this finding. First, subjects with reduced synaptic dopamine levels or receptor density would be expected to have a greater number of available binding sites or a lower baseline tonic signalling, thus supporting a larger impact of tonic D₂ receptor activation by dopamine agonists (Martins et al., 2017). However, this view is opposed by observations that dopamine agonists have higher affinity for presynaptic autoreceptor D₂ isoforms than post-synaptic receptors (Usiello et al., 2000). Thus, a second explanation is that at *low doses*, these drugs may have largely inhibitory effects. According to this view, dopamine agonists enhance activation of presynaptic D₂ autoreceptors in dopamine releasing neurons through auto-regulation. This may counter-act the post-synaptic effects and diminish dopamine release in individuals with higher D₂ receptor availability (Martins et al., 2017).

In line with this notion, *lower* doses of cabergoline (1.25 mg) and pramipexole *decreased* reinforcement learning following the presentation of rewarding outcomes (Frank and O'Reilly, 2006b) and decreased choice bias towards stimuli most predictive of reward (Pizzagalli et al., 2008a). It therefore seems that these results are in line with pre-synaptic effects at D₂ receptors and inhibition of dopamine transmission at low doses via regulatory feedback. Remarkably however, similar doses of these drugs

simultaneously increased aversive value of punishing outcome (Cavanagh et al., 2014) and feed-back-related negativity (FNR) ERP signal (Santesso et al., 2009). This pattern of results is thus similar to the findings reviewed with L-DOPA and APTD, in which the same dopamine manipulation led to opposite effects on reward versus penalties. Surprisingly, the authors do not suggest potential mechanisms underlying this effect; however, one possibility is that effects on other neurotransmitter systems (e.g. adrenergic or serotonergic) could mediate these distinct neurobehavioural effects.

1.6.3.5 ***Dopamine precursor depletion: acute phenylalanine and tyrosine depletion, alpha-methyl-para-tyrosine***

With the acute phenylalanine and tyrosine depletion method (APTD), individuals drink a mixture of amino acids which are deficient in phenylalanine and tyrosine. The result of APTD is that it reduces plasma levels of phenylalanine and tyrosine and dopamine release in striatum (Leyton et al., 2000; Roiser et al., 2005).

In line with reduced dopamine availability, the behavioural effects of APTD in healthy volunteers include reduced contentment, reduced betting rate in a reward decision-making task and increased apathy (McLean et al., 2004a). This is paralleled with disrupted reward- and punishment-based learning or expected value (McLean et al., 2004a). This pattern of APTD-induced disturbances in processing of reward and punishments in healthy volunteers mirrors that previously reported in currently depressed patients (Murphy et al., 2003) and thus APTD has been used as a behavioural model of depression (Leyton et al., 2000). Indeed, individuals with a history of depression seem to be more sensitive to dopamine depletion than healthy controls, leading to more pronounced APTD-induced changes in behaviour. Whereas APTD led to reduced risk-taking decision making in remitted MDD individuals (Roiser et al., 2005), APTD did not cause healthy controls to bet less overall, rather, to increase bets more slowly (McLean et al., 2004b). In accordance with findings at the behavioural level, neuroimaging studies have found that APTD decreases activity in the caudate and NAcc activation during reward anticipation (Bjork 2014).

In some studies it is interesting that the same effect of DA depletion leads to differential effects on rewards versus penalties (i.e. differential effect on valences).

APTD increased learning rate from negative outcomes in a probabilistic selection task (Cox et al., 2015) and shifted sensitivity from rewards to punishment so that there was an increased learning from punishments, but not rewards in a reversal learning task (Robinson et al., 2010). However, in the latter study, this effect was only found in females. This is an interesting finding and may point to the gender bias typical in MDD (see Section 1.1.2) as well as highlighting the importance of including gender as a covariate in studies examining pharmacological modulation of dopamine on reward.

Another important consideration is that the effect of APTD on reward processing is moderated by genetic variability in catechol-o-methyltransferase (COMT) Val158Met genotype. Homozygotes of 158Val have relatively lower levels of dopamine than 158Met carriers (Chen et al., 2004; Saville et al., 2014). Whereas APTD increased immediate bias for reward in 158Val homozygotes, it had the opposite effect on 158Met carriers. Thus, inter-individual differences in dopamine baseline levels are important to address.

Taken together, there seems to be a strong consensus that decreases in dopamine availability by APTD leads to reduced responses to rewards, yet it may also increase penalty-related processing. Behavioural findings are supported with expected reductions in striatal BOLD activity during reward tasks.

1.6.3.6 ***Dopamine synthesis enhancement (L-DOPA)***

In contrast to APTD, L-DOPA has quite the opposite effect and PET studies in humans have shown that L-DOPA increases striatal dopamine synthesis (Black et al., 2015). Indeed, effects of APTD on diminished reward processing are reversed by previous administration of L-DOPA (Leyton et al., 2007).

The majority of behavioural studies using 100-150 mg doses of L-DOPA have shown that it is associated with increased learning rate (Chowdhury et al., 2013b), increased performance in instrumental tasks involving monetary gains (Pessiglione et al., 2006) and increased propensity for risky decisions in trials involving potential gains (Beierholm et al., 2013; Rutledge et al., 2015). Two studies however showed that the same dose of L-DOPA had no effect on reward processing (Apitz and Bunzeck, 2014; Wittmann and D'Esposito, 2015). This result could be related to a number of factors, such as ceiling effects, low statistical power or variable responses due to baseline

states of dopamine. This is another illustration of how using pharmacological manipulation in conjunction with genotype variability may be a way to characterise the dopamine dose-response curve more carefully.

Even without behavioural effects, acute L-DOPA does enhance neural representations of reward (a pattern which has also been shown with SSRI, DRI and SNRI drug classes). An increase in striatal and midbrain VTA activations has been demonstrated during the anticipation phase (Guitart-Masip et al., 2012) and in the NAcc and ACC during the consummation phase (Oei et al., 2012b). This was in the opposite direction to D₂ antagonist haloperidol (3 mg) during subliminal presentation of sexual stimuli (Oei et al., 2012b). One study found that L-DOPA (100 mg) enhanced striatal activity for punishment, but not reward cues (Wittmann and D'Esposito, 2015). Given that this result unlikely reflects an ineffective dose, it could be that there was enhanced overall cue salience in punishment relative to reward trials. In terms of prediction error, L-DOPA increased bilateral VS and putamen activation for both reward and penalty-related PEs relative to dopamine antagonist haloperidol (Pessiglione et al., 2006). These results suggested that dopamine availability drives PE-based neural coding in the human brain.

A final and key consideration when taking together the results of L-DOPA manipulations on reward processing is that it is also the precursor of other catecholamines such as noradrenaline. Thus, an important question is to what extent the effects in the L-DOPA studies described above are attributable to dopamine versus noradrenaline. Future studies that account for L-DOPA's effect on noradrenaline levels are needed.

1.6.3.7 *Limitations and recommendations for reward neuropharmacology research*

A placebo controlled design with healthy controls facilitates the interpretation of drug effects on reward and penalty processing, whilst minimising potential confounds. The evidence reviewed is generally of high quality, however, pharmacological manipulation of reward and penalty processing still faces a variety of methodological challenges. These can impinge upon mechanistic models and translation from animal

to human models. The main challenges and suggested solutions are summarised in Table 1.9. In addition to the listed issues, another important consideration is the effects that pharmacological agents can have on cerebral blood flow (CBF), described below.

Effects on cerebral blood flow and considerations for functional imaging of pharmacological effects

The formation of the BOLD signal is described in detail in Imaging Methods Section 2.1.2. In brief, the basic principle is that brain activity is linked to metabolic activity in the brain and indicated by changes in blood oxygen. Specifically, the haemodynamic response (HDR), (i.e. the increase in oxygen-rich blood delivery to active brain areas) underlies the BOLD contrast, and the magnetic properties of oxyhaemoglobin and deoxyhaemoglobin increase and decrease the MR signal respectively (Thulborn et al., 1982). This series of events is referred to as neurovascular coupling and is the assumption that relates BOLD signal to putative underlying neural activity. In pharmacological fMRI, BOLD signal could change by either direct effects of the drug on neural activity or via non-specific effects on cerebral metabolic activity or on the vasculature itself (Iannetti and Wise, 2007; Wise and Tracey, 2006b). These potential effects are illustrated in Figure 1.17. The neuronal response (left) is of interest, yet it may be masked by drug or disease influences on signalling or vascular response. In rows 4 and 5, the BOLD response is confounded by these factors, and in rows 2 and 3, the BOLD signal is a true, accurate representation of underlying activity.

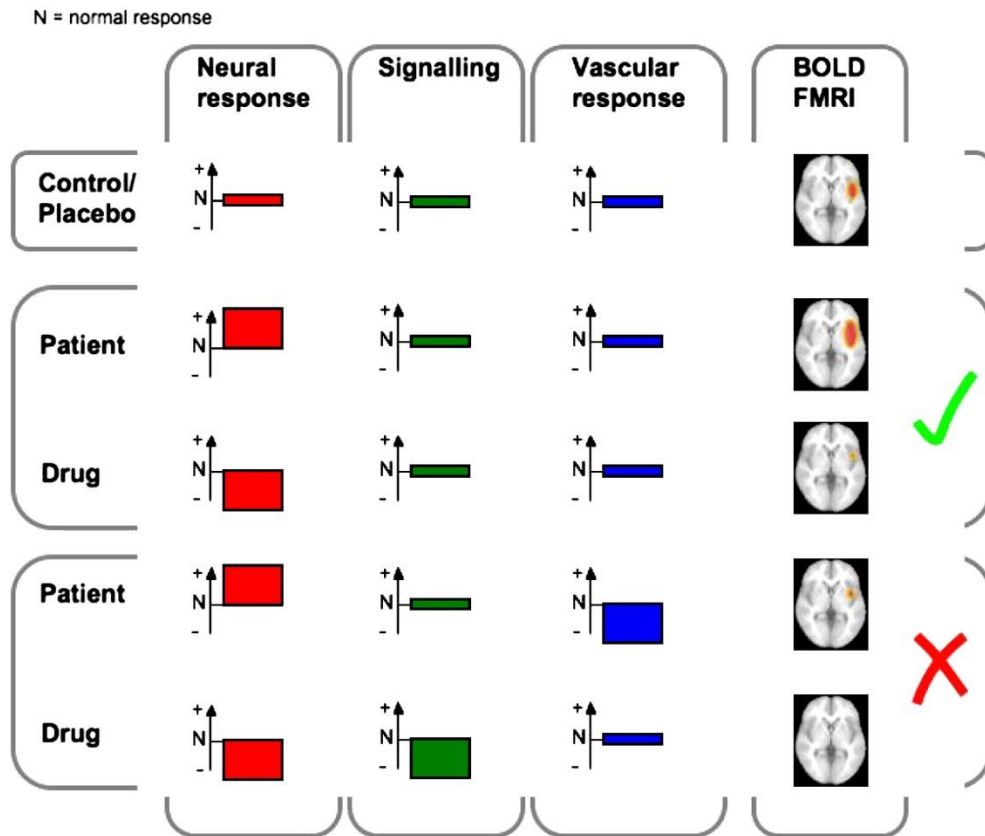


Figure 1.17. Potential confounds for the generation of BOLD fMRI signal. Taken from Iannetti and Wise, (2007) with permission.

Effects of dopamine antagonists on CBF

An increasing number of studies have employed MRI modality arterial spin labelling (ASL) in order to assess quantitative changes in cerebral blood flow induced by dopamine antagonists (Detre et al., 2012; Handley et al., 2013). The methods and principles of ASL are described in detail in Imaging Methods Section 2.1.2.7, however, in brief; ASL is an instrument to assess the effects in vivo of psychopharmacological medication on brain perfusion (regional cerebral blood flow (rCBF)). Unlike perfusion techniques in PET, that require the invasive infusion of radioactively labelled contrast agents, MR-based ASL uses radio frequencies and magnetic field gradient pulses to magnetically label blood (or ‘arterial spins’). This allows the non-invasive quantification of local perfusion in the brain, with greater spatial and temporal resolution and applicability than PET (Detre et al., 2012; Detre and Wang, 2002). Indeed, ASL techniques may be more easily integrated in a within subjects crossover study design (as the one used in this thesis) due to their radiation-

free properties, presenting no issue of exposure (Detre and Wang, 2002). Moreover, several test-retest studies have shown that ASL perfusion measurements are highly reproducible across minutes, hours, days and weeks (Chen et al., 2010; Floyd et al., 2003; Parkes et al., 2004).

Although several studies have examined the effects of acute and long-term administration of dopamine antagonists in schizophrenia (Goozee et al., 2014), comparatively fewer (n=6) have examined changes in CBF in healthy volunteers (Fernandez-Seara et al., 2011; Goldman et al., 1996; Goozee et al., 2014; Handley et al., 2013; Mehta et al., 2003; Michels et al., 2016; Viviani et al., 2013). A robust and consistent finding is that single dose of dopamine antagonists have potent effects in increasing striatal blood flow in healthy samples (Fernandez-Seara et al., 2011; Goldman et al., 1996; Goozee et al., 2014; Handley et al., 2013; Mehta et al., 2003; Michels et al., 2016; Viviani et al., 2013). Handley and colleagues (2012) used ASL to investigate the effects of single dose haloperidol (3 mg) or aripiprazole (10 mg) on rCBF in a placebo-controlled, repeated measures design in healthy males. Both drugs significantly increased rCBF in the putamen and ACC relative to placebo, whilst aripiprazole was also associated with rCBF decreases in posterior cingulate, superior frontal and superior parietal areas. Another study examined the effects of acute 10 mg metoclopramide using ASL (Fernandez-Seara et al., 2011). They also found significant increases in perfusion in the striatum (particularly the putamen), as well as the thalamus. Decreases in perfusion were found in the insula and anterior temporal lobe. A recent study used a randomised crossover, placebo-controlled design in 25 healthy adults to examine acute dose quetiapine (DA antagonist) and pramipexole (dopamine agonist) on resting CBF (Michels et al., 2016). Relative to placebo, quetiapine enhanced CBF in the putamen and caudate nucleus, as well as the supplementary motor area, insular and prefrontal cortex, whilst reducing perfusion in occipital and cerebellar cortex. In a similar fashion, pramipexole increased CBF in the caudate nucleus and putamen, with reduction in thalamus, cerebellum and visual areas. Taken together, there seems to be common dopaminergic effects of dopamine antagonists in striatal regions, but also differences in prefrontal, insular and cingulate regions. This could stem from the different receptor profiles of the drugs, which is discussed in detail below.

Potential mechanisms underlying increases in striatal CBF

The mechanisms by which dopamine antagonist medications lead to alterations in rCBF remain unclear, although some suggestions have been formulated. The concept of neurovascular coupling suggests that rCBF reflects metabolism whereby regions of increased post-synaptic activity require more blood oxygen supply, and perfusion is modulated in order to meet this demand (Logothetis et al., 2001; Logothetis and Pfeuffer, 2004; Logothetis and Wandell, 2004). These haemodynamic processes may reflect synaptic processes rather than spiking activity, with postsynaptic metabolism making the greatest contribution (Lauritzen, 2001). Given that most dopamine antagonists have a common (high) affinity and antagonism to D₂ receptors, it follows that changes occur in areas most densely populated with D₂ receptors, such as the striatum (Goozee et al., 2014). Indeed, dopamine D₂ receptors are primarily found in OFC, and insular cortical areas, in the striatum (caudate putamen, nucleus accumbens, globus pallidum) the central amygdala, and in the midbrain (substantia nigra and ventral tegmental area) (Ott et al., 2014; Rosenkranz and Grace, 2002). Antagonism in striatal D₂ receptors would be expected to change neurotransmitter turn over and subsequently alter metabolism and perfusion. It has been proposed that rCBF increases reflect increased presynaptic synthesis of dopamine and dopamine release as a result of decreased negative feedback via autoreceptors. A possible interpretation is that blockade of D₂ receptors in the striatum potentially results in disinhibition of D₂ receptor containing medium spiny neurons (Fernandez-Seara et al., 2011). In contrast, the observed decreases in rCBF in frontal and temporal regions by some D₂ antagonist drugs (Handley et al., 2013) could reflect either excitatory or inhibitory down-stream effects from striatal regions (Goozee et al., 2014).

However, CBF may also be influenced by the effects on astrocytes (glial cells that also modulate blood flow requirements by dilation or constriction of arterioles) and the drug's activity at other receptors (Attwell, et al., 2010). For example, D₃ receptors are within the same family as D₂ receptors and are located on astroglial cells (Choi et al., 2006), which regulate regional blood flow. There is evidence that D₃ agonists can cause vasoconstriction by binding to these sites. Thus, as some antipsychotic drugs have affinity for D₃ receptors (Girgis et al., 2015; Stahl, 2013), D₃ antagonism could potentially lead to vasodilation and increases in CBF.

The picture is complicated further by the fact that other neurotransmitters have effects on vascular receptors. Several of the dopamine antagonists with antidepressant properties (e.g. quetiapine, amisulpride) also have affinity for serotonergic receptors. There is evidence that serotonin binds to receptors on the vasculature as well as astrocytes, thereby causing vasoconstrictive effects (Cohen et al., 1996). Moreover, in the study by Michels and colleague (2016), mentioned above, the authors suggested that quetiapine's effects on reducing CBF in occipital cortex could be related to 5-HT_{1A} and _{2A} receptors in these regions. In sum, the different patterns of rCBF modulation by the dopamine antagonists reviewed could reflect how their varying receptor affinity profiles alter (i) disinhibition of D₂ receptors (densely populated in the striatum), (ii) astroglials, and (iii) serotonin receptors (densely populated in cortical regions).

Taken together, drugs with broad receptor profiles could have highly variable effects on underlying vasculature, thereby altering baseline CBF, interfering with neurovascular coupling and the interpretation of a drug on BOLD signal. To ensure that BOLD signal changes are not a result of disturbed neurovascular coupling integrity, different methods can be applied. For example, it is possible to use imaging modalities such as arterial spin labelling (see Section 2.1.2.7 for more details), to quantify changes in CBF which are not confounded by changes in cerebral blood volume (CBV) or cerebral metabolic rate of oxygen (CMRO₂) (Wise and Tracey, 2006a). Despite ASL having lower signal-to-noise ratio than BOLD (Jahng et al., 2005) and less brain coverage (Wang et al., 2011a; Wang et al., 2004; Wang et al., 2003), it has excellent test-re-test reliability (Wang et al., 2011b) and is sensitive to slow changes in CBF which are commonly reported with drug administration (Aguirre and Detre, 2012; Aguirre et al., 2005). Several studies have now controlled for global and regional changes in CBF at rest when analysing BOLD data and this is a vital step towards understanding if the effects of a drug are indeed neuronal. For dopamine antagonists, it seems particularly important to control for changes in baseline striatal blood flow in the analysis of BOLD data. An even better approach, which some groups are beginning to develop, is the collection of task-related ASL and BOLD simultaneously. Although, parallel imaging is still not optimal for deep brain structures such as the striatum due to a loss of signal-to-noise ratio with double-echo sequences (Ivanov et al., 2017). Other methods have also been addressed, such as the use of control tasks, including a placebo condition and assessing vascular reactivity

via breath holds. Whilst it is common for studies to address these issues, it is rare that more than one of these factors is considered in a single study.

In spite of these challenges, pharmacological manipulation is an invaluable tool to improve cause-effect based models of reward and penalty processing.

Table 1.9. Limitations and potential recommendations for future neuropsychopharmacology research on reward and penalty processing in healthy controls and depression. Main points adapted from Martins et al., (2017).

Limitations	Potential solutions
Difficulty in making predictions and interpretations of drug effects as there is a low availability of safe and licensed drugs targeting specific enzymes or receptors. This makes it difficult to differentiate the role and contribution of each type of receptor in reward and penalty processing	Further testing for approval of more specifically targeted drugs (dopamine in particular).
Unclear assumptions of pre- and post-synaptic action, in relation to specific doses; potential sources of noise or confounding (e.g. neuropsychological and genotypic inter-individual differences that are related to baseline differences in dopamine receptors/reuptake and bioavailability of enzymes that degrade dopamine) which affect the dynamics of drug response (Wichers et al., 2008).	Factors known to vary dopamine baseline levels should be controlled when assessing response to dopaminergic modulation (e.g. sex, menstrual cycle (Dreher et al., 2007; Jacobs and D'Esposito, 2011), genetic variants (catechol-O-methyl transferase (COMT) Val(158)Met polymorphism, MET/MET, VAL/VAL, VAL/MET (Wichers et al., 2008)). More knowledge about individual genetic and biological variation in association with reward processing may add to the process of prediction and improvement of treatment response to antidepressant medication. Quantitative measures of dopamine baseline levels (e.g. PET neuroimaging, eye-blink rate) (Jongkees and Colzato, 2016).
Unequal number of studies investigating reward processing relative to penalty processing and difficulty in comparing between tasks (e.g. phase, feedback modality, performance-contingent feedback, contrasts of interest).	More studies investigating penalty-related processing and use of standardised tasks e.g. MID and contrasts of interest (Knutson et al., 2001).

Difficulty in differentiating the effects of pharmacological challenges on phasic, tonic or both modes of dopamine release as well as the interaction between these processes.	Potential use of computational simulation of the cortico-striatal network in order to create mechanistic predictions about the effect of the drug on synaptic signalling, auto-receptor, auto-regulatory mechanisms. Examining drugs with different mechanisms of action (at the receptor level) in the same paradigm/framework. Need for interdisciplinary pharmacogenetics-psychophysiological-neuroimaging-behavioural approaches.
Effects of drugs on cerebral blood flow which may compromise the reliability and interpretation in BOLD fMRI studies.	Acquire quantitative measures of changes in CBF (utilising ASL, PET) (Alsop et al., 2015; Detre et al., 2012; Detre and Wang, 2002; Detre et al., 2009). Use of control tasks to assess the drug's non-specific effects on the haemodynamic response (e.g. breath-hold, hypercapnic BOLD fMRI)(Wise et al., 2013) .

1.6.3.8 ***Other interventions: psychological, combined psycho-pharmacological and brain-targeted.***

In addition to pharmacological modulation of reward, there are a small selection of studies which have investigated how psychological and brain-based interventions alter the behavioural and neural correlates of reward and penalty processing in healthy and depressed individuals. The results of a comprehensive literature review are presented in Table 1.10 and include psychological interventions (Behavioural Activation (BA) (n=5), Cognitive Behavioural Therapy (CBT) (n=3), Mindfulness Based Cognitive Therapy (n=1), Mental Imagery (n=1), and combined psychological and pharmacological treatment (n=1). A detailed explanation of the principles, theory and implementation of BA and CBT interventions can be found in Section 1.1.5.2, and brief descriptions of the interventions used in the studies reviewed are provided in the caption of Table 1.10. Whilst four studies examined the ability of baseline reward processing to predict clinical outcomes (Burkhouse et al., 2016; Carl et al., 2016b; Vrieze et al., 2013b; Walsh et al., 2016), another set of studies completed experimental sessions at two time points to examine pre-to-post changes in behaviour, neural activity and depressive symptom improvement (Dichter et al., 2009; Linke and Wessa, 2017; Mori et al., 2016b; Straub et al., 2015). I will begin by summarising the studies

which predicted response to treatment from baseline (i.e. T1 only) reward processing measures.

A key theme among these studies is whether a more normative pattern of reward-related responding (i.e. more similar to healthy controls) or whether a more divergent neural pattern to controls at baseline predicts greater improvement in clinical symptoms post-treatment. Carl et al., (2016) demonstrated that at a behavioural level, patients who exhibited faster responses to obtain rewards fared better after treatment. This suggests that BA may be an effective treatment for patients with relatively preserved hedonic responses or capacity to anticipate incentives. Similar results were found at a neural level, as patients with a more normative pattern (greater sustained activation in the ACC from MID task run 1 to run 2) were more responsive to treatment (Carl et al., 2016b). The ACC is critically involved in controlling social approach-avoidance behaviours (Challis and Berton, 2015) as well as detecting the significance or incentive salience of external stimuli (Phan et al., 2005). Thus, capacity to sustain ACC activation in the face of rewards may be an important predictor of response to a therapeutic approach that specifically targets motivationally salient aspects of the environment. A similar finding has also been reported using a brain-based intervention and changes in resting-state functional connectivity between key regions of the brain's reward network. Twenty sessions of MRI-guided repetitive transcranial magnetic stimulation (rTMS) to the dorsomedial prefrontal cortex showed that MDD patients who responded to treatment had greater pre-treatment VTA-NAcc-vmPFC connectivity at rest compared to non-responders (Downar et al., 2014). However, as both these studies only used measures at one time point (T1), post-treatment neuroimaging is required to evaluate whether the same brain regions that are predictive of treatment response are those that show recovery of functioning after treatment.

The majority of studies suggest that patients with greater deficits in reward processing may be better candidates for BA, CBT and combined psycho-pharmacological treatment (Burkhouse et al., 2016; Rice et al., 2015; Vrieze et al., 2013b; Walsh et al., 2016). At a behavioural level, reduced pre-treatment reward learning predicted/increased odds for persisting MDD diagnosis at 8 weeks (odds ratio = 7.84), after controlling for depressive and anxious symptoms at baseline (Vrieze et al., 2013b). Rice et al., (2015) showed that lower reward seeking at baseline was associated with

greater decline in depressive symptoms pre-to-post intervention with CBT with a focus on increasing reward processing, and CBT with a focus on reducing negative beliefs. An EEG study showed that patients with a reduced RewP at baseline (i.e. more different to HC) were more likely to respond to treatment (greater pre-to-post CBT reduction in depressive symptoms) among individuals with comorbid depression-anxiety but not in the anxiety only group (Burkhouse et al., 2016). Another study used a similar analysis framework to Carl et al (2016) by evaluating sustained activity, however this time with a focus on fronto-striatal functional connectivity (i.e. taking into account the network nature of the reward system) (Walsh et al., 2016). The majority of findings showed that a more divergent pattern of pre-treatment fronto-striatal connectivity during reward anticipation and outcome was associated with superior MDD treatment response to BA. Thus, as a key component of CBT and BA is to increase engagement with valued behaviour (Dimidjian et al., 2011), it could be that these therapies function particularly well for individuals with greater deficits in reward-related fronto-striatal connectivity. BA in particular, may be effective in normalising deficits associated with anticipatory processes, effort valuation and decision-making to initiate goal-directed behaviour. This highlights the potential of personalised interventions for MDD. That is, individuals with greater alterations in connectivity and capacity to sustain connectivity in the brain's reward network may be better suited for interventions that target reward network functioning and related behaviours, whilst other interventions may be more affective to patients with different neural connectivity patterns. To evaluate this framework, larger-scale studies which assess patient responses to several kinds of treatment modalities are needed. Moreover, if both perspectives are taken into consideration (i.e. more normative vs. more divergent neural patterns) it may be that there is an optimal threshold for response to treatment, in which patients must display deficits, but also some preservation of reward function to allow for the optimal remediation of such deficits.

Another important theme that emerged from the review is temporality, or the conceptualisation of hedonic capacity in MDD as a decreased capacity to sustain response to rewards over time (Heller et al., 2013; Pizzagalli et al., 2008c). In support of this framework, two studies examined changes in reward-related neural activity across two runs of the MID task (i.e. sustained activation) as well as aggregating across the two runs (i.e. global responses) (Carl et al., 2016b; Walsh et al., 2016).

These studies demonstrated that the MDD group experienced a significant decrease in NAcc activation during reward outcomes (Carl et al., 2016b) and fronto-striatal connectivity during reward anticipation and outcome (Walsh et al., 2016) from the first to the second task run relative to healthy controls. There was greater sensitivity in predicting clinical response to treatment in MDD patients when examining patterns of neural attenuation compared to global values (Walsh et al., 2016). This suggests the importance of examining temporal changes in neural activity as an MDD endophenotype that is relevant for predicting antidepressant response. With reference to the previous discussion, it is interesting to note that the majority of findings (which took into account brain activation over time), showed that patients whose brain connectivity patterns were more divergent than controls responded better to treatment (see Table 1.10 for details).

The most valuable studies are those which completed experimental sessions at two time points and could thereby examine pre-to-post intervention changes (Dichter et al., 2009; Linke and Wessa, 2017; Mori et al., 2016b; Straub et al., 2015). A study in adolescents with subthreshold depressive (sD) symptoms found that a significant reduction in depressive symptoms with 5-7 weeks of BA was paralleled by increased activity in the ventrolateral PFC and angular gyrus during loss anticipation, whereas this was not the case in the healthy control group (Mori et al., 2016b). Given the role of the vLPFC in inhibitive control of negative emotions and cognitions (Payer et al., 2012), the authors suggested that this finding may reflect an improved ability of sD individuals to regulate negative emotions using cognitive strategies post-treatment.

In contrast, the neuroimaging studies by Dichter et al., (2009) and Straub et al., (2015) used behavioural paradigms that did not assess penalty-related processing and exclusively assessed reactions to rewarding stimuli. After a longer period of 15 weeks BA therapy, MDD patients showed increased paracingulate gyrus activity during reward selection, and increased activity in the caudate nucleus, cingulate gyrus and insula during reward anticipation. A normalisation of striatal activity during reward anticipation is consistent with preclinical and clinical models of MDD and anhedonia that implicate dysregulation of the mesostriatal pathway in the pathophysiology of MDD (Anisman et al., 1979; Nestler and Carlezon, 2006; Treadway et al., 2012). It is also consistent with the framework that the mechanisms of action of various antidepressant interventions are to improve motivational striatal functioning

(Argyropoulos and Nutt, 2013; Halaris et al., 1975; Nestler, 1998). However, as in Mori et al., (2016), the neural findings were not supported by significant changes in task-related behavioural responses to rewards. Thus, BA results in recovery of function in brain regions related to processing of rewards without a change in behavioural performance. A lack of change in behaviour may reflect the fact that the tasks used are more sensitive to neural activation than to behavioural performance (Knutson et al., 2008). This is in line with other studies reporting no baseline differences in task-related behavioural performance between MDD and healthy volunteers (Knutson et al., 2008; Stoy et al., 2012a). Another explanation could be lack of power to detect a difference due to the small sample size, or, perhaps prolonged treatment is required for motor-related changes in RT and accuracy, unlike subjective ratings of self-evaluated motivation. Indeed, performance-based measures provide more objective measures than self-report because they allow for the measurement of cognitive biases or alterations that may not be open to introspection (Harmer et al., 2009c; Rawal et al., 2013). Moreover, the use of performance-based measurements reduces the chance that the associations with depression are due to shared method variance. This can occur when the same individual rates a risk factor (e.g. cognitive bias) and an outcome (e.g. clinical symptoms).

Interestingly, two studies demonstrated a reduction in frontal (OFC, subgenual ACC), striatal (caudate nucleus) and/or limbic (amygdala, hippocampus) regions during reward feedback post BA intervention in MDD patients relative to healthy volunteers (Dichter et al., 2009) and waitlist MDD group (Straub et al., 2015). The decrease in caudate activation after BA in the MDD group (in alignment with symptom improvement) is somewhat counterintuitive and bears replication. The authors suggest that this result could stem from the mismatch of the caudate's role in learning cue-outcome contingencies and that win outcomes were not directly contingent on behavioural performance in the wheel of fortune task. In response to missed win outcomes, BA increased activation in the OFC, a region involved in the affective evaluation of rewards, motivation, decision-making and processing violations of expectancies (Dichter et al., 2009). Thus, it could be that pre-treatment MDD patients do not expect positive outcomes, with BA inducing a change in reward expectancy such that a missed win post-treatment violates their expectancies to a greater degree, reflected by greater OFC activation relative to pre-treatment (Dichter et al., 2009).

Improvements in depressive symptoms was strongly correlated with changes in sgACC activation and individual expressions of pre-CBT treatment sgACC activation predicted individual therapeutic responses relative to a MDD waiting condition (Straub et al., 2015). These findings are in line with previous reports (albeit using emotional stimuli as opposed to monetary rewards) of linear-load response activity in the ACC and greater response to CBT treatment. In sum, activation of fronto-striatal regions, commonly reported as relevant in depression (Zhang et al., 2013), changed with amelioration of depressive symptoms.

There were two behavioural studies in healthy controls investigating pre-to-post changes in reward approach across CBT-r (with a focus on reward processing), CBT-nb (with a focus on reducing negative beliefs), MBCT (Rice et al., 2015) and a rewarding mental imagery intervention (Linke and Wessa, 2017). Rice and colleagues showed that the only intervention explicitly focused on enhancing attention and sensitivity to reward (CBT-r), was associated with a post-intervention decrease in depressive symptoms and increase in reward seeking behaviour in the Cambridge gambling task (versus CBT-nb and MBCT). Moreover, degree of change in reward seeking was associated with improvement in depressive symptoms and this association differed significantly to the comparison group. Baseline reward seeking behaviour also moderated depressive symptoms change. Thus, the results suggest that reward-seeking may be the basis for symptoms change in the course of a treatment which emphasises on identifying and focusing on positive events and memories and rational reward-seeking behaviour. The implication is that incorporating reward-related activities into prevention programs may enhance efficacy. However, this interpretation must be acknowledged in the context that this study was a non-randomised design and this limits the ability to make causal inferences due to the potential of differences on key confounders across groups. Moreover an interesting avenue for further work is whether CBT with a focus on reducing reactivity to negative events in general (as opposed to negative self-beliefs) would lead to changes in sensitivity to loss responses in a behavioural task.

The behavioural study using a mental imagery intervention similarly showed that an improvement in depressive symptoms (NB: in a healthy control sample) was accompanied by increased wanting, reward sensitivity, faster approach to positive edibles and activities in the mental imagery group relative to the wait condition at

follow-up (Linke and Wessa, 2017). A neural mechanism underlying these behavioural changes could be understood by the findings of Sulzer and colleagues (Sulzer et al., 2013). They used a healthy control sample to show that mental imagery of sexual and romantic scenes increased activity in the substantia nigra and ventral tegmental area (SN/VTA). This suggests that rewarding imagery is a robust method of SN/VTA self- (endogenous) up-regulation. Moreover, subjects who received veridical neurofeedback about activity in the VTA, improved their ability to up-regulate SN/VTA, co-activated other dopaminergic regions (NAcc, caudate, hippocampus), and showed increased connectivity along the nigrostriatal pathway (VTA-caudate, VTA-putamen) at rest compared to control subjects who received sham feedback. Given that BOLD activity in these areas has been previously correlated to dopamine levels using positron emission tomography (Dubol et al., 2017a; Schott et al., 2008), BOLD signal increases may reflect firing of dopaminergic neurons. Further research should address longer-term behavioural and neural consequences of mental imagery interventions within the same research framework as strategies for persistent regulation could have useful applications for the treatment of depression. As these studies were completed in healthy control samples only, it will also be important to examine effects in MDD, as individuals with diminished reward reactivity prior to treatment may have more room for improvement.

With reference to the previous discussion on reward and penalty modulation by antidepressant medications, it is important to highlight that 7 of 8 interventions studies reviewed here recruited un-medicated MDD patients. This is a key advantage as it avoids medication confounds in the interpretability of the psychological intervention findings. However, the results of these studies must be considered within the context of their limitations (see Table 1.10). A number of studies did not have an untreated/non-intervention comparison group (e.g. placebo, waitlist, psychoeducation-only control group), or other treatment group. It is therefore unknown whether functional brain changes in the MDD group were due to intervention or to other variables, such as spontaneous improvement of symptoms over time; or specific to the intervention type as opposed to psychotherapy in general. Moreover, from the reward-based intervention literature I have reviewed, all studies examined pre-to-post treatment changes, but not intermediate steps or ‘early-on-in-treatment’ changes. Harmer and colleagues have shown that early changes in the perception and neural

response to positive social stimuli with antidepressant medication treatment is related to subsequent improvement in depression severity (Godlewska et al., 2016; Shiroma et al., 2014; Tranter et al., 2009). Indeed, a classification-based data analysis demonstrated that if an early change in positive processing is not seen with antidepressant drug treatment, patients have little chance of responding to this later in the treatment course (Tranter et al., 2009). Therefore, to examine whether reward processing changes using *psychological* interventions align with Harmer's model of *pharmacological* interventions (Harmer et al., 2009a), it would be useful to conduct longitudinal studies examining reward processing at baseline (pre-treatment), early in treatment, post-treatment, and 3-6 month follow-up. A greater conceptual issue, especially with regards to the CBT interventions, is the broad number of therapeutic components and techniques covered in treatment. Thus, it is not clear what the active component for successful treatment response and normalisation of neuropsychological responses to reward is. To this end, one can appreciate the relative simplicity and specificity of findings, and greater experimental control in an acute pharmacological intervention design, as utilised in this thesis.

Table 1.10. Overview of intervention studies examining the modulation of reward and penalty processing by (i) Behavioural Activation Treatment for Depression (BA or BATD) (ii) Cognitive Behavioural Therapy (CBT) (iii) Mindfulness Based Cognitive Therapy (MBCT) (iv) Mental Imagery (v) Combined, non-standardised psycho-pharmacological treatment. **BATD sessions:** series of structured units that (a) educate patients about MDD and provide a rationale for the treatment approach; (b) assess and monitor baseline activity levels; (c) develop individualised goals according to patients' values and initiate a multi-layered plan to achieve these goals; and (d) monitor, support, and reward accomplishing behavioural goals. **CBT sessions:** psychoeducation; strategies to reduce negative beliefs (cognitive restructuring); behavioural procedures (e.g. exposure to fears, behavioural activation); self-esteem enhancement; problem solving; emotion-regulation; acute crisis management; and relapse prevention. **CBT with reward processing** (Rice et al., 2015): CBT with a focus on identifying and focusing on positive events and memories in addition to decision making training. **CBT to reduce negative self-beliefs** (Rice et al., 2015): CBT with focus on identifying, evaluating and challenging negative thoughts. **MBCT:** increasing awareness and acceptance of bodily sensations, thoughts and feelings. **Mental imagery sessions:** imagining positive emotions, affirmative thoughts, and pleasurable sensations associated with positive food and activities.

*Experimental session at baseline/pre-treatment (T1) or both pre-treatment and post-treatment (both T1 and T2). ** Time interval between intervention and experimental session. ***Significant after correction for multiple comparisons with FWE, FDR, Bonferroni or permutations. Relative to comparison group (column 7 from the left) unless otherwise specified.

Intervention	Paper	Sample type/size	T1/T2 /both? *	Time after intervention**	Study Design	Comparison group/control	Intervention description	Task	Behavioural effects	BOLD***	EEG	Limits
Behavioural Activation Treatment for Depression	Mori (2016)	Healthy control (n=15) (Low (BDI<10) versus subthreshold depression (sD: n=15) (High BDI>10)	Both T1 and T2.	5-7 weeks.	Mixed design (within subject pre-post intervention for high BDI groups, pre-post scan for low BDI/HC	Low BDI group (healthy control) no intervention.	sD group received 5 weekly BA sessions.	MID.	↓ Depressive symptoms in individuals with sD receiving BA. N.s change in behavioural performance or in self-evaluated motivation.	↑ vIPFC and angular gyrus in sD group receiving BA Vs.HC group during loss anticipation.	-	Small sample size. No sham condition control group. No untreated/non-intervention comparison group (i.e. waitlist subthreshold depression group). No other treatment group (e.g. psychoeducation).

Behavioural Activation Treatment for Depression	Dichter (2009)	Healthy control (n=15) versus MDD (n=12).	Both T1 and T2.	102 days (mean).	Mixed design (within subject pre-post intervention for MDD group, pre-post scan for HC group)	HC group (matched).	MDD group received 11.4 (mean) weekly BA sessions.	Wheel of Fortune task .	<p>↓ Depressive symptoms: 75% MDD treatment responders. N.s change in task-related behavioural responses.</p> <p>↓ BDI total scores and anhedonia subscales. Pre-treatment anhedonia severity and task-related RT predicted response to treatment: ↑ pre-treatment anhedonia and ↑ decline in RT from run1 to run2 during reward trials showed greater ↓ symptom with BATD.</p>	<p>↑ paracingulate gyrus during reward selection, ↑ L dorsal striatum (caudate nucleus), L cingulate gyrus, R insula during reward anticipation, ↓ R caudate nucleus, L paracingulate and orbital frontal gyri during reward feedback, relative to HC group</p> <p>Sustained AAC activation during reward outcomes predicted treatment response. ↑ sustained ACC, more responsive to BATD treatment.</p>	-	<p>No placebo/wait-list control group (therefore unknown whether functional brain changes in the MDD group due to BA intervention or to other variables, such as spontaneous improvement of symptoms over time).</p> <p>No comparison treatment condition. Therefore not clear whether predictors of treatment response are specific to BATD or psychotherapy in general. No post-treatment brain scans.</p>
	Carl (2016)	Healthy control (n=20) versus MDD (n=33).	T1 only.	-	-	HC group (matched).	8-15 weekly BATD sessions.	MID (2 runs).			-	

Walsh (2017)	Healthy control (n=20) versus MDD (n=33).	T1 only.	-	-	HC group (matched).	8-15 weekly BATD sessions.	MID (2 runs).	↓ depressive symptoms.	<p>↑ L caudate and R paracingulate gyrus pre-treatment global connectivity in MDD group during reward anticipation (i.e. more divergent from controls) predicted greater improvement in BDI scores/BATD treatment response.</p> <p>↑ attenuation of pre-treatment connectivity (i.e. greater drop-off in connectivity between MID run 1 and 2, more divergent from HC) in R frontal medial cortex and paracingulate gyrus during reward anticipation; left NAcc and paracingulate gyrus during reward outcome, predicted improved response to BATD.</p> <p>↓ attenuation of</p>	-	No penalty trial in the MID task. No comparison treatment condition. No post-treatment brain scans. Mild depression scores (HAMD>15).
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[illegible]

										association differs significantly to comparison group.	
CBT	Straub (2015)	MDD group (medication--ive). MDD-Intervention (n=10) and MDD-waiting list (n=12) groups.	Both T1 and T2.	5 weeks.	Mixed design (within subject pre-post intervention for intervention and waitlist MDD groups)	MDD waiting list group.	MDD Intervention group received 4-6 weekly 90 minute treatment sessions by 2 clinical psychologists.	MID.	<p>↓ clinical symptoms in MDD-Intervention group. N.s change psychometric/brain activity in MDD-waiting list.</p> <p>↓ amygdala, hippocampus and sgACC during reward outcome (win>no win). Pre-to-post sgACC activation change correlated with pre-to-post and pre-to-follow-up symptom improvement. Individual expressions of pre-treatment sgACC activation related to pre-to-follow-up therapeutic response.</p>	-	Small sample size. No healthy control comparison group.

	Burkhouse (2016)	Comorbid MDD+anxiety (n=22) versus anxiety only (n=30) group.	T1 only.	-	-	Anxiety only group.	Once-weekly sessions manualized individual CBT for 12 weeks.	Guessing reward task (reward and penalty trials).	↓ depressive symptom (68% response to treatment).	-	↓ RewP ERP at baseline associated with greater pre-to-post CBT reduction in depressive symptoms in MDD-anx group but not the anxiety only group.	Unclear which CBT technique resulted in symptom improvement and functional changes in reward processing. Small sample. No pure MDD/ HC comparison group. Open-label (nonrandomised CBT) so cannot conclude that clinical improvement specific to CBT. No post-treatment brain scans.
CBT for negative beliefs	Rice (2015)	Healthy control (n=256). (CBT with reward: n=43); CBT with negative belief focus: (n=49); MBCT: (n=49); Comparison: (n=82)	Both T1 and T2.	8 weeks.	Non-randomised, Mixed design (within subject pre-post intervention for three intervention groups).	CBT-reward focus, MBCT intervention groups and no intervention group (normal PSHE lessons)	8 (50 min) weekly sessions delivered by educational psychologists at school	Cambridge Gambling Task (CGT)	N.s change in depressive symptoms or reward seeking behaviour from pre-post intervention. ↓ baseline reward seeking associated with greater decline in depressive symptoms with this CBT intervention and the CBT-reward intervention.	-	-	Sample sizes in each intervention group relatively small. Non-randomised design limits ability to make causal inferences (potential differences on key confounders across groups).
MBCT	Rice (2015)	Healthy control (n=256).	Both T1 and T2.	8 weeks.	Non-randomised, Mixed	CBT-reward focus,	8 (50 min) weekly	Cambridge Gambling	↑ depressive symptoms and n.s change in	-	-	Sample sizes in each intervention group relatively small.

		(CBT with reward: n=43); CBT with negative belief focus: (n=49); MBCT: (n=49); Comparison: (n=82).			design (within subject pre-post intervention for three intervention groups).	CBT-negative belief focus intervention groups and no intervention group (normal PSHE lessons)	sessions delivered by educational psychologists at school	g Task (CGT)	reward seeking behaviour from pre-post intervention. MBCT and CBT-negative beliefs did not differ.			Non-randomised design limits ability to make causal inferences (potential differences on key confounders across groups).
Mental Imagery	Linke (2017)	Healthy controls (n=30) (pre-selected for low reward sensitivity)	Both T1 and T2.	Not Clear. Hints 2 weeks.	Mixed design (within subject pre-post intervention, pre-post wait-list for HCs).	Wait condition.	15 minute training every second day during a 2 week period.	Probabilistic Reward task. Approach Avoidance Task.	↓ depressive symptoms, ↑ wanting, reward sensitivity, ↓ RT (faster approach) to positive edibles and activities in Mental Imagery group relative to wait condition.	-	-	No MDD sample. Waitlist control condition (therefore do not know if observed effects resulted from mental imagery exercises or non-specific features of the intervention). No longer-term follow-up.
Combined, non-standardised Psycho-pharmacological treatment	Vrieze (2013)	Healthy control (n=63) versus MDD inpatient (n=79) sample (high and low anhedonia)	T1 only.	-	-	HC group; MDD patients with low anhedonia.	8 weeks treatment with range of psychological and pharmacological interventions.	Probabilistic reward task	↑ reward learning ability in MDD; normalised to HC level. ↓ reward learning over time in high anhedonic Vs. low-anhedonic patients. ↓ pre-treatment reward learning predicted/ increased odds	-	-	Psycho-pharmacological treatment was not standardised. Medicated MDD subjects, therefore medication confound. No penalty trials in reward task.

for persisting
MDD diagnosis
at 8 weeks
(odds ratio =
7.84), after
controlling for
depressive and
anxious
symptoms at
baseline.

1.6.3.9 *Interim summary*

In summary, this section has reviewed how various interventions (pharmacological, psychological, and brain-based interventions), normalise neurocognitive mechanisms of reward and penalty processing in depression. I have outlined evidence in favour of a cognitive neuropsychological model of antidepressant action (Harmer et al., 2009b) in the normalisation of negative emotional biases and reward processing. The evidence suggests that an acute or seven day dose of agents acting on dopamine receptors (e.g. amisuplride and bupropion) is sufficient to enhance neural signals to reward but not behaviour or learning; whilst SSRIs enhance neural and behavioural signals of reward after a prolonged period. It is important to understand the temporal effects of antidepressants on reward processing as it may have implications for the use of antidepressants in targeting anhedonia early versus late in treatment. This has implications for how antidepressants may enhance PE (e.g. as in (Graf et al., 2016; Scholl et al., 2017)), and be used to improve reward-related learning to enhance the effectiveness of psychological treatment such as behavioural activation.

Given that dopamine plays an important part in the symptoms of anhedonia (Wise, 2008) and D₂ antagonists have been traditionally seen as relatively ineffective at treating this symptom dimension (or even proposed to exacerbate it) (Danna and Elmer, 2010; Mizrahi et al., 2007; Wise, 2008), it is counterintuitive that some low doses of dopamine antagonists potentiate striatal responses. Indeed, there is a complex picture for the effects of D₂ antagonism and agonism on reward and penalty processing. The effects may depend on (i) pre-versus post-synaptic effects, which is related to (ii) drug dose and (iii) inter-individual variation (e.g. genetic variation which affects availability of dopamine receptors and regulators (DAT, COMT) that influence dopamine concentration and signaling. Another consideration is that many of the ‘dopaminergic drugs’ which I reviewed have a broader pharmacological profile, acting on serotonin and other systems, and this may also be a source of variation. Nevertheless, pharmacological manipulation of the dopamine system is valuable for improving the cause-effect based models of reward and penalty processing.

The neural correlates of pre-treatment reward processing seem to predict response to both pharmacological and psychological interventions in depressed samples. However, there is a need to examine whether patients who show the greatest resolution of

reward/penalty processing early in treatment are more likely to respond with continued treatment, thereby aligning with Harmer's model. There are few studies examining the normalisation of reward, and especially, penalty-related neural responses by psychological (BA and CBT) therapies. However, the evidence thus far points to an association between symptom improvement and normalisation of anticipatory responses. Further longitudinal imaging studies are needed, using appropriate comparison groups (e.g. healthy control, alternative therapies) to elucidate the time-scale of normalisation responses at different phases of reward processing (e.g. do responses to reward outcomes normalise before responses to reward anticipation?).

It is also important to note the inherent challenges in the comparison of reward and penalty processing across interventions. Although an attempt has been made to summarise the trends, one must consider various factors that limit the ability to make direct comparisons between studies results: (i) sample type (healthy control sample only, both HC and depressed patient groups); (ii) study design and control condition (within-subjects cross-over, between-subjects parallel design, placebo-controlled); (iii) medication duration (acute, prolonged); (iv) administration (oral, intravenous); (v) task (active versus passive, phase, valence, contrasts of interest). Nevertheless, the studies reviewed incorporate well-validated behavioural and neural assessments of reward (and to a lesser degree) penalty mechanisms. These designs allow the elements altered by an intervention to be elucidated and are an essential step in delineating how interventions produce effects on symptoms (Kraemer et al., 2002). Indeed, objective neural and behavioural measures may be more sensitive and accurate in detecting cognitive change than self-report measures (Harmer et al., 2009c; Rawal et al., 2013) and are thus used in this thesis.

Another important consideration is that acute pharmacological intervention designs, as used in this thesis, provide greater simplicity and specificity of findings, and greater experimental control than long-term pharmacopsychological interventions. Acute experimental medicine studies are also more easily applicable, and less costly than the implementation of randomised control trials. Among the pharmacological literature, dopamine antagonists show sensitivity to reward system and potential in depression. They are particularly interesting candidates with dopamine antagonism (which can either increase or decrease striatal dopamine levels) and high affinity for serotonin 5-HT receptors. However, there is limited evidence in depression and a need for more

studies showing modulation of reward, and especially penalty-related function in healthy and depressed samples using randomised placebo-controlled designs. Taken together, this sets the premise for the investigation in this thesis, which I will continue to introduce in the following sections.

1.7 Dopamine antagonist: Lurasidone

Lurasidone, the compound utilised in this study, has high affinity for dopaminergic and serotonergic receptors. Lurasidone was selected for this study because it is the most recently licensed dopamine antagonist with antidepressant properties and there is no information with regards to its effects on brain reward signalling (Goldberg et al., 2017; Loebel et al., 2014a; Loebel et al., 2014c; Nelson et al., 2015; Nierenberg et al., 2015; Suppes et al., 2016a; Suppes et al., 2016b). In the sections below I first review evidence from randomised controlled trials (RCTs) that lurasidone is an effective antidepressant agent and secondly describe how its receptor profile may be associated to its antidepressant properties. I then go on to describe the lack of systems-level knowledge about lurasidone to date, which sets the premise for the aims and objectives of the thesis in Section 1.8.

1.7.1 Lurasidone: general information

Lurasidone is a benzisothiazol derivative and has been classified as a second generation atypical antipsychotic (SGA or AAP) (Greenberg and Citrome, 2017; Ishibashi et al., 2010). It has received regulatory approval for the treatment of schizophrenia in the US, Canada, the EU, Switzerland, and Australia, and also for bipolar depression in the US and Canada (Greenberg and Citrome, 2017). As shown in Figure 1.18, lurasidone has a particular pharmacological profile. In addition to its principal antagonist activity at dopamine D2 and serotonin 5-HT_{2A} receptors, lurasidone has distinctive 5-HT₇ antagonistic activity and displays partial agonism at 5-HT_{1A} receptors, as well as modest antagonism at noradrenergic α_{2A} and α_{2C} receptors. Lurasidone is devoid of antihistaminic and anticholinergic activities. In Section 1.7.3 below, I go on to describe how this profile may be related to its antidepressant activity and side effects. Lurasidone is administered once daily within the range of 40–160 mg/day for schizophrenia and 20–120 mg/day for bipolar depression, and its pharmacokinetic profile requires administration with food (Fornaro et al., 2017; Greenberg and Citrome, 2017; Jaeschke et al., 2016).

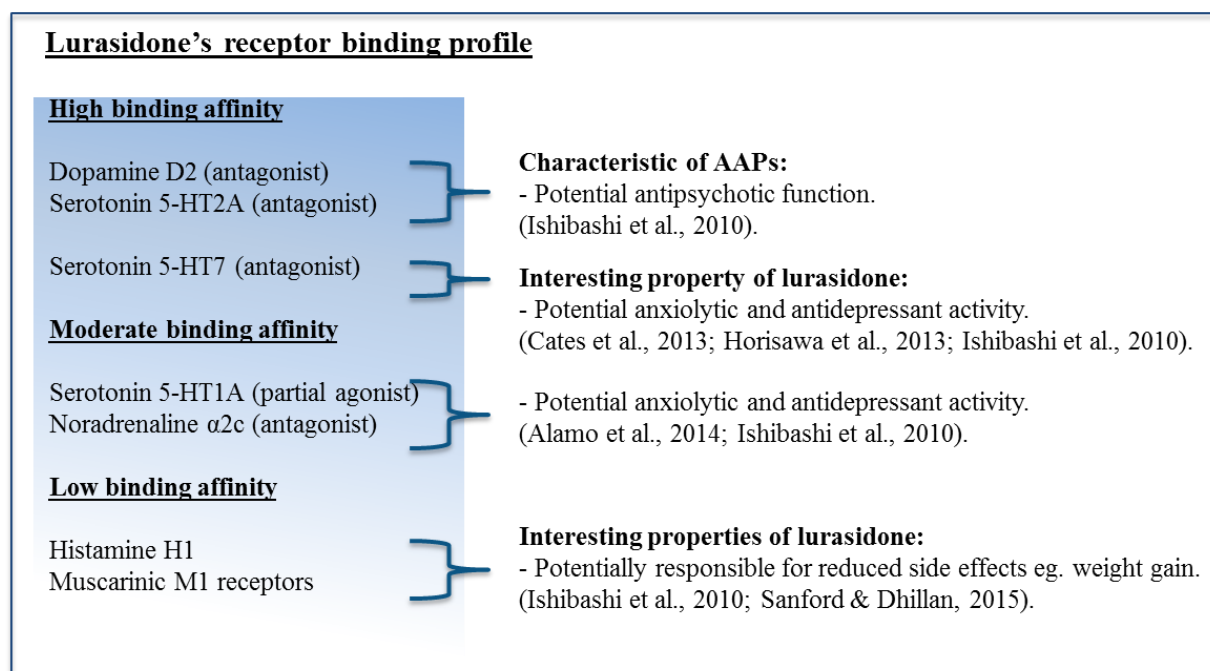


Figure 1.18. Lurasidone's receptor binding profile.

1.7.2 Lurasidone's antidepressant efficacy: Evidence from randomised control trials.

There have been several randomised control trials (RCTs) to evaluate lurasidone's efficacy in adults with bipolar depression as well as depression with and without mixed features. Patients with a major depressive episode were randomly assigned to receive six weeks of double-blind treatment with one of two flexible dose ranges of lurasidone (20–60 mg) (n = 166) or 80–120 mg/day (n = 169) or placebo (n=170) (Loebel et al., 2014b). Both the 20–60 mg/day lurasidone group ($p < .0001$; effect size = 0.51) and the 80–120 mg/day lurasidone group ($p < .001$; effect size = 0.51) showed significantly improved Montgomery-Asberg Depression Scale (MADRS) total scores compared with the placebo group. The reduction in depressive symptoms was found by the second week of treatment and was maintained after six weeks of treatment (Loebel et al., 2014b). Importantly, post-hoc analyses from the same RCT, have also found that lurasidone is effective at treating unipolar depression with and without mixed features (McIntyre et al., 2015; Suppes et al., 2016b) and not only as monotherapy (Loebel et al., 2014b), but also adjunct to classical mood stabilisers (Loebel et al., 2014c; Suppes et al., 2016a). A particular advantage of lurasidone is that it does not increase susceptibility to weight gain like other antidepressant AAPs

such as quetiapine and olanzapine (Citrome et al., 2014). Taken together, the results of double-blind trials indicate that lurasidone demonstrates a favourable benefit/risk ratio for the treatment of depression, with ‘single-digit’ Number Needed to treat (NNT) (indicating significant efficacy) scores and ‘double-digit’ or higher Number Needed to Harm (NNH) scores (indicating high tolerability) (Loebel and Citrome, 2015).

Indeed, in a recent meta-analysis of short- to medium-term RCTs of 4-16 weeks, for pharmacological therapies in depressed adults (Taylor et al., 2014), it was found that lurasidone monotherapy yielded similar efficacy to olanzapine, quetiapine, selective serotonin reuptake inhibitors (SSRI), lithium, and tricyclic antidepressants (TCA). Additionally, there was a significant reduction in anxiety symptoms, and improvement of patient-rated functional impairment and quality of life. The adjunctive lurasidone therapy was well-tolerated and the discontinuation of the medication due to adverse effects was comparable to placebo. Table 1.11 summarises data comparing the relative efficacy and tolerability of lurasidone to other drugs in the treatment of depression (Jaeschke et al., 2016; Taylor et al., 2014).

The evidence that lurasidone is an effective antidepressant as monotherapy has additional translational value as many individuals with depression are treated with several pharmacological interventions at once (McIntyre et al., 2013). This is the case even when monotherapy is the most adequate first-line approach (Fornaro et al., 2016), and evidence that polypharmacy may have detrimental effects on overall treatment adherence (Fornaro et al., 2015). Future RCTs need the inclusion of active compound alternatives, such as fixed versus standard dose head-to-head comparisons of lurasidone to quetiapine and olanzapine. Moreover, long-term double-blind extension studies are needed to examine the effects of lurasidone after six week treatment.

Table 1.11. Relative efficacy and tolerability of lurasidone to other drugs for bipolar depression. Taken from Jaeschke et al., (2016) with permission.

Outcome #1: Primary efficacy (change in scores on the MADRS or HAM-D)		
Lower efficacy	Similar efficacy	Higher efficacy
–	<ul style="list-style-type: none"> • Aripiprazole • Lamotrigine • Lithium • MAOI • Olanzapine • Quetiapine • Risperidone • SSRI • TCA • Valproate • Ziprasidone • Olanzapine + fluoxetine • <i>placebo</i> 	–
Outcome #2: Primary tolerability (switch to mania)		
Lower risk	Similar risk	Higher risk
<i>placebo</i>	<ul style="list-style-type: none"> • Aripiprazole • Lamotrigine • Lithium • MAOI • Olanzapine • Quetiapine • Risperidone • SSRI • TCA • Valproate • Ziprasidone • Olanzapine + fluoxetine 	–
Outcome #3: Secondary efficacy (response)		
Lower efficacy	Similar efficacy	Higher efficacy
<ul style="list-style-type: none"> • Aripiprazole • Ziprasidone • Olanzapine • Lamotrigine • Lithium • SSRI • TCA • MAOI • <i>placebo</i> 	<ul style="list-style-type: none"> • Quetiapine • Risperidone • Valproate • Olanzapine + fluoxetine 	–
Outcome #4: Tolerability (withdrawal)		
Lower risk	Similar risk	Higher risk
–	<ul style="list-style-type: none"> • Aripiprazole • Lithium • MAOI • Olanzapine • Quetiapine • Risperidone • SSRI • <i>placebo</i> 	<ul style="list-style-type: none"> • Olanzapine + fluoxetine

MAOI, monoamine oxidase inhibitors; SSRI, selective serotonin reuptake inhibitors; TCA, tricyclic antidepressants.

1.7.3 **Linking the pharmacological profile of lurasidone to antidepressant mechanism of action and side effects**

There have been several animal studies in lurasidone, linking its action at various receptors to its potential psychological effects (summarised in Figure 1.18). Indeed, Ishibashi et al., (2010) used behavioural experiments and animal models of depression and anxiety in rats to show that lurasidone demonstrates potent anxiolytic-like and antidepressant-like activity, with a low propensity for motoric or extrapyramidal symptom side effects. The olfactory bulbectomy model was used to investigate the antidepressant-like effects of lurasidone. Specifically, rodents had an operation that disrupted the limbic-hypothalamic axis and led to behavioural changes, of which many resemble changes seen in depressed patients. In this test, lurasidone showed similar antidepressant effects to the tricyclic antidepressant imipramine by significantly reducing the number of lines crossed in an enclosed space (Ishibashi et al., 2010). In an animal model of anxiety (social interaction test), lurasidone significantly prolonged the time spent in social interaction compared with the control group.

Dopaminergic activity may play a major role in anti-depressant effects, (Brugue and Vieta, 2007), both by lurasidone's direct activity at D₂ receptors and indirectly through the effects that serotonergic receptors have on dopamine release.

First, lurasidone has a loose D₂ postsynaptic occupancy (fast dissociation time) compared to alternative antipsychotics and this feature may make lurasidone an optimal drug for treating mood disturbances (Brugue and Vieta, 2007). Indeed, in line with the framework of Juckel et al (2006), FGAs³, such as haloperidol, worsen negative symptoms such as amotivation and apathy by additional suppression of DA activity. In contrast, SGAs (e.g. quetiapine, olanzapine, lurasidone) are proposed to improve negative symptoms by virtue of their comparatively reduced blockade of D₂ receptors and faster rate of dissociation from D₂ receptors (Stahl, 2013) (although

³ Within this discussion it is important to note that the field has largely moved away from the FGA/SGA distinction because (i) a broad two level categorisation may be overly simplistic as within these groups there is a marked difference in their receptor profiles and (ii) a focus on mechanisms 'neuroscience-based nomenclature' (<https://www.nbn2.com/>).

lower occupancy may be an artefact of the fast dissociation). Thus, SGAs may provide a sufficient and permanent input of striatal dopamine to maintain drive and affective responsivity. Experimental evidence in support of this theory has come from the effects of both antipsychotic drug classes on striatal response in the MID task (Juckel, 2016; Juckel et al., 2006). A more ecologically valid study assessed positive and negative affect in the daily life of patients taking antipsychotic medication classified as loose (olanzapine; n=35) or tight (haloperidol, risperidone; n=74) binding, based on the drug's dissociation at the D₂ receptor (Lataster et al., 2011). The study found a significant three-way interaction between binding group (loose vs tight), D₂ receptor occupancy estimates and experience of positive and negative affect in daily life. Specifically, higher levels of estimated D₂ receptor occupancy was related to decreased feelings of positive affect and increased feelings of negative affect, whilst for loose-binding-agent users, this association was not significant. These findings suggest that lurasidone's mood stabilising effects could, in part, be mediated by allowing sufficient dopamine availability by faster rate of dissociation from D₂ receptors.

A second consideration is that dopamine levels may be maintained by the effects that serotonergic receptors have on dopamine release. Indeed, as part of Juckel et al.'s framework, it was also suggested that SGAs' increased 5-HT affinity (with antagonism of 5-HT_{2A} receptors increasing striatal DA release) also promotes sufficient dopamine availability. The role of 5-HT in increasing dopamine release has been shown experimentally with lurasidone. Specifically, Huang et al., (2012) tested whether lurasidone's 5-HT_{1A} partial agonism and/or 5-HT₇ antagonism, contributed to the ability of lurasidone to enhance dopamine release. They showed that lurasidone, like other atypical antipsychotics, produced a dose-dependent increase in DA efflux in the prefrontal cortex, hippocampus and NAcc of rats. In addition, a 5-HT_{1A} receptor antagonist partially blocked the lurasidone-induced dopamine efflux, whereas a 5-HT_{1A} agonist and a 5-HT₇ receptor antagonist potentiated the effect of lurasidone to increase DA efflux, especially in the prefrontal cortex. These findings suggest that 5-HT_{1A} receptor agonism and affinity to 5-HT₇ is involved in the effect of lurasidone on dopamine efflux, and this could form part of its actions on mood and cognition improvement (Huang et al., 2012). In a similar way, 5-HT_{2A} receptors are present on presynaptic dopamine neurons, and blockade of these receptors increases dopamine

release (Yatham et al., 2005). Lurasidone, like other AAPs blocks 5-HT_{2A} receptors and this is expected to increase dopamine levels, as has been found previously with olanzapine and quetiapine (Ichikawa et al., 2002; Koch et al., 2004).

Beyond dopamine, anti-depressant effects may also be mediated directly via activity at serotonergic 5-HT₇, 5-HT_{1A}, 5-HT_{2A}, and noradrenaline α_{2C} receptors (Brugue and Vieta, 2007; Fornaro et al., 2017; Fountoulakis et al., 2015; Yatham et al., 2005). For example, 5-HT₇ knock-out mice show antidepressant-like behaviour and selective 5-HT₇ antagonists show antidepressant-like action by decreasing immobility time in the tail suspension and forced swim test (models of depression) (Wesolowska et al., 2006). It has been suggested that 5-HT_{1A} activation mediates the effects of SSRIs on neurogenesis which is considered to underlie antidepressant-like effects with prolonged SSRI administration (Santarelli et al., 2003). As mentioned above, lurasidone has high affinity for 5-HT₇ and 5-HT_{2A} receptors (antagonist), and moderate binding affinity to 5-HT_{1A} (partial agonist) and α_{2C} (antagonist), and as these receptors are involved in depression (Brugue and Vieta, 2007), they may contribute to the effects of lurasidone in animal models of depression.

Last of all, lurasidone's low affinity for histamine H₁ and muscarinic M₁ receptors is proposed to underlie lurasidone's minimal central nervous system (CNS) depressant side effects such as sedation and somnolence as well as reduced risk of weight gain and cardiovascular side effects (Ishibashi et al., 2010). The higher tolerability and a lower risk of unpleasant side effects with lurasidone is particularly pronounced when compared with other agents (e.g. olanzapine) that have major impacts on metabolic syndrome and weight gain, especially in youth (Ketter et al., 2011; Correll et al., 2010). In this manner, it is important to not overlook the indirect effects that a more tolerable drug, such as lurasidone, can have on mood in longer-term treatment regimens (Brugue and Vieta, 2007).

Taken together, there seems to be a complex interaction between the major neurotransmitter systems without a single target being either necessary or sufficient to elicit an antidepressant effect (Fountoulakis et al., 2015), and lurasidone may work at several receptors at once in order to bring about antidepressant effects (Fornaro et al., 2017).

1.7.4 Lurasidone: Further work needed to understand antidepressant action at a systems level

Despite the neurochemical theories of lurasidone's antidepressant mechanism of action, there is not a unified systems-level investigation of lurasidone's mechanism of action in humans. Indeed, to date, there have been no pharmacoinaging studies investigating the modulation of neurocognitive mechanisms by lurasidone. As discussed in Section 1.1.3 and 1.5, reward and penalty processing are central to depressive disorders and thus this thesis was interested in utilising a neuropsychological framework to investigate the modulation of reward and penalty systems by lurasidone. The research approach, main aims and objectives of this thesis are introduced in the following section.

1.8 Research Approach: Aims and Objectives

In the introductory chapter of the thesis, I have reviewed the current state of evidence regarding depression, reward/penalty processing and dopamine antagonists. While many neuroimaging studies address two elements (e.g. depression and reward; depression and dopamine antagonists; reward and dopamine antagonists), there are few experimentally controlled study designs to date which have examined these three elements in unison: using dopaminergic drugs to probe the association between neural reward signalling and depression. Figure 1.19 summarises these matters schematically and highlights the gaps in the existing literature that this thesis aims to address. Below, I summarise the main arguments that lead to the conception of this study, before presenting the specific aims and hypotheses.

1.8.1 Summary of main rational for this thesis' research approach

MDD is a common, recurrent and disabling mental illness which is poorly treated by currently prescribed drug therapies. Many individuals with MDD do not respond to available antidepressant drugs, and patients that do respond can experience side effects and a delay in several weeks before a therapeutic effect is observed. Often multiple treatment cycles with different drugs are required in order to identify an effective therapy. The discovery of treatment tools that target putative mechanisms of illness in depression – such as hyposensitivity to rewarding and hypersensitivity to aversive events - is thus a clinical priority.

As discussed in Section 1.5, there is now a rich literature examining the brain correlates of reward and penalty-related processing deficits in depression and this association meets Bradford-Hill Causality criteria (Hill, 1965) for: (i) specificity (ii) plausibility (iii) biological gradient and (iv) temporality. Yet, the field requires further experimental evidence (i.e. interventions which show results consistent with the association), as this would provide the next important step to establishing the role of neuropsychological reward and penalty processing as a causal event in depressive illness (Hill, 1965; Höfler, 2005).

Previous studies have successfully used experimental intervention designs to test whether acute dose anti-depressants modify brain processes implicated in depression (Section 1.6) (Arnone et al., 2009; Godlewska et al., 2012; Harmer et al., 2017;

Harmer et al., 2009a; Harmer et al., 2003b; Harmer et al., 2009c; McCabe et al., 2010; Murphy et al., 2009; Norbury et al., 2007; Rawlings et al., 2010; Scholl et al., 2017). Since a direct link has been found between reduced mid-brain transporter density and neural activity during reward processing within the mesolimbic pathway in healthy and depressed human participants (Dubol et al., 2017b), dopaminergic compounds may provide a promising way to manipulate fronto-striatal reward pathways (Chowdhury et al., 2013a; Harmer et al., 2017; Jocham et al., 2011; McCabe et al., 2010; Pessiglione et al., 2005; Vrieze et al., 2013a).

Surprisingly, however, very few studies have used dopaminergic drugs to probe the association between neural reward signalling and depression. Recently, Admon et al., (2017) showed that a single-dose of the dopamine receptor antagonist amisulpride normalised reward processing by increasing reward-related striatal activation and corticostriatal connectivity in depressed individuals. This effect is thought to result from transient increases in dopamine signalling at low amisulpride doses (Admon et al., 2017; Schoemaker et al., 1997). Strengthening of striatal functioning through dopamine antagonists has been shown before in healthy volunteers (Handley et al., 2013; Mehta et al., 2003) and is presumed to occur through presynaptic D₂/D₃ autoreceptor blockade (Fernandez-Seara et al., 2011; Goozee et al., 2014).

It may seem counterintuitive that some antipsychotics are antidepressant given that D₂ antagonism (a central feature of all antipsychotics) is known to suppress reward-related striatal activation, for example, with haloperidol (Oei et al., 2012b; Pessiglione et al., 2006; Pleger et al., 2009b). However, olanzapine (Tohen et al., 2014; Tohen et al., 2003), quetiapine (Suppes et al., 2014; Suttajit et al., 2014) and lurasidone (Loebel et al., 2014a; Loebel et al., 2014c; Nelson et al., 2015; Suppes et al., 2016b), which are efficacious antidepressants, differ from haloperidol in their broader profile, including greater serotonergic action. Indeed, blockade of serotonergic 5-HT receptors (5-HT_{1A}, 5-HT_{2A}, 5-HT₇) stimulates striatal dopamine release and in addition to this, serotonergic neurons directly impact upon reward (and predominantly aversive) processing (Boureau and Dayan, 2011; Cohen et al., 2015; Hayashi et al., 2015; Huang et al., 2012; Inaba et al., 2013; Li et al., 2016; Liu et al., 2014). However, there are few studies that have assessed modulation of loss anticipation and feedback with antidepressant drugs. The evidence thus far points to a pattern of blunting of aversive events with acute administration of selective serotonin reuptake inhibitors (SSRIs)

(Macoveanu, 2014; Macoveanu et al., 2014; Macoveanu et al., 2013; McCabe et al., 2010), but crucially also with D₂ antagonists that have anti-depressant properties (amisulpride (Admon et al., 2017) and aripiprazole (Bolstad et al., 2015)).

These findings raise the intriguing possibility that dopamine antagonists with antidepressant properties may exert their effects via *reward* and/or *penalty* signal normalisation.

The purpose of this thesis is to investigate the effect of a novel dopaminergic agent⁴, lurasidone, on a fronto-striatal-limbic network implicated in reward and penalty processing and prediction error in depression. In doing so, this thesis aims to extend preliminary findings that dopamine antagonists may exert their effects via reward or penalty signal normalisation in depressed individuals (Admon et al., 2017).

Lurasidone was selected because it is the most recently licensed dopamine antagonist with antidepressant properties and there is no information with regards to its effects on brain reward signalling (Goldberg et al., 2017; Loebel et al., 2014a; Loebel et al., 2014c; Nelson et al., 2015; Nierenberg et al., 2015; Suppes et al., 2016a; Suppes et al., 2016b). Therefore, as this is the first fMRI study of lurasidone in humans to date, this thesis aims to further our knowledge about lurasidone's potential antidepressant mechanism of action and this information may in turn help to develop and refine new treatment targets. In other words, using an experimental medicine design such as the one used in this study, could help identify relevant compounds which could then be tested further in using longer-term follow up, or a new target for engagement in future drug development studies. On a broader scale, this thesis aims to contribute to what is called 'rational treatment advances' for psychiatric disorders based upon pathophysiologic and etiological processes.

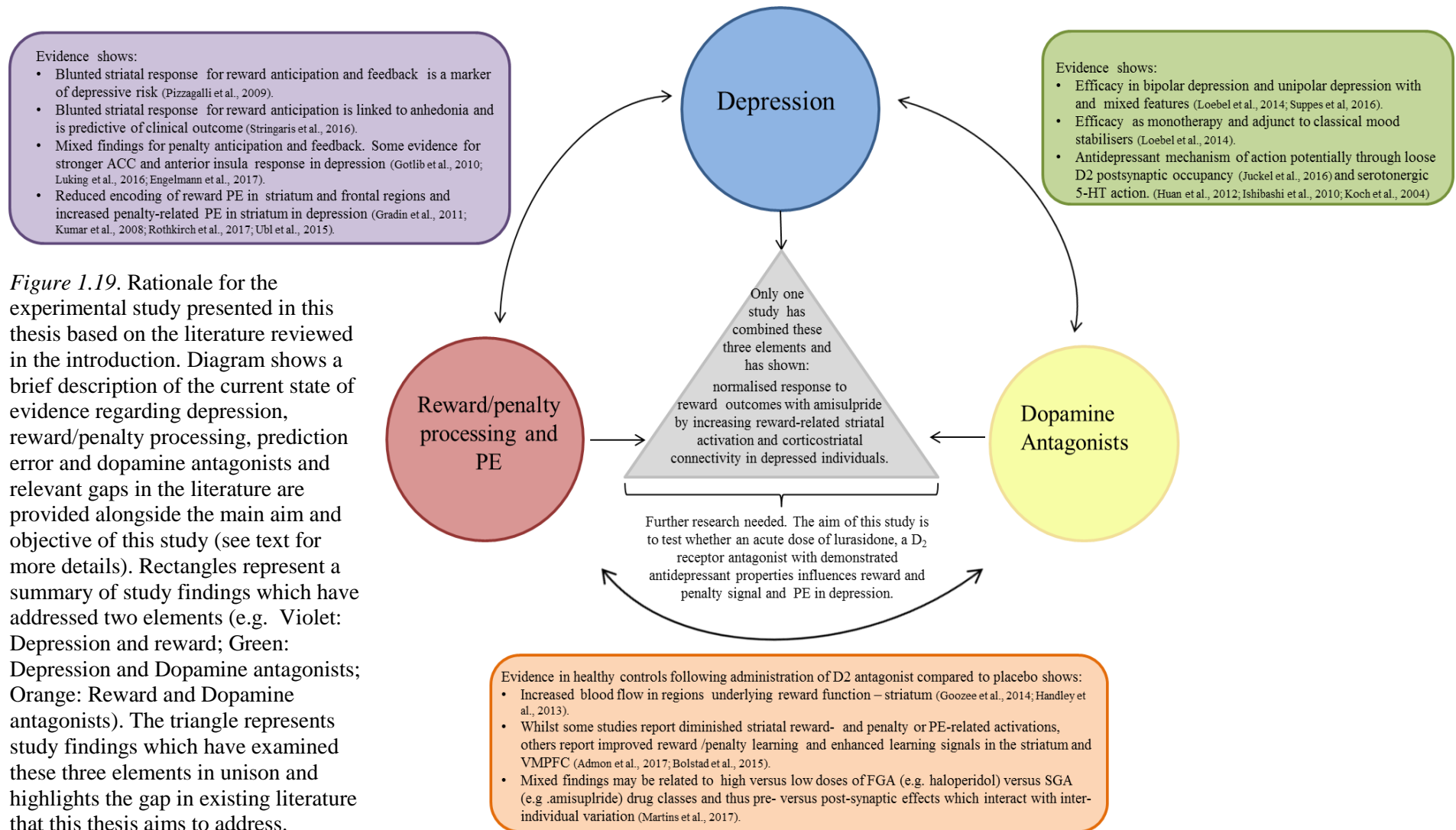
To summarise, this thesis probes the association between neural reward/penalty signalling and depression using a dopaminergic agent and aims to (i) further our

⁴ For the purpose of the thesis, I will use the term 'dopaminergic agent' to refer to pharmacological agents that transiently increase or decrease dopamine signalling. I prefer the term 'dopaminergic agent' to 'antipsychotics' or 'dopamine antagonists' because of the varied effects these agents have on dopamine levels through post-and pre-synaptic antagonism. Indeed, the term 'dopamine antagonist' may be misleading when low doses of, for example, amisulpride, in fact increase dopamine signalling through presynaptic autoreceptor blockade, whilst, high doses reduce dopamine availability (Schoemaker et al., 1997).

understanding of the (causal) involvement of reward and penalty mechanisms in depression (ii) elucidate the antidepressant-mechanism of action of lurasidone; and (iii) define clear therapeutic targets.

In order to probe the association between neural reward/penalty signalling and depression, we utilise an acute dose of 20 mg lurasidone and a randomised, placebo-controlled cross-over study with BOLD fMRI during a reward task and arterial spin labelling imaging at rest acquired on two separate occasions per individual.

Approximately half of the participants (n=22) were randomly selected to receive lurasidone on the first visit and the placebo on the second, and the other participants (n=21) received placebo on the first visit and lurasidone on the second visit. A one-week washout period was used to avoid carry-over effects, based on the reported 18h half-life of lurasidone 40 mg (Sunovion, 2013). A detailed description of the study design can be found in Methods Section 3.3. Since symptoms of MDD fall on a continuous dimension (Angst et al., 2000; Ayuso-Mateos et al., 2010), we recruited subjects across the range of depression severity, including healthy volunteers (n=20), as well as people meeting subthreshold (n=9) and full-criteria MDD (n=11). This research approach is in line with the Research Domain Criteria framework (Morris and Cuthbert, 2012) (e.g. as in (Stringaris et al., 2015b) where symptom levels are related to the brain measurements). It also does justice to findings concerning the genetic underpinnings of common mental illness (Plomin et al., 2009) as well as current approaches to understanding neural system perturbation in a dimensional way (Matthews and Hampshire, 2016). To rule out any confounding medication effects (Kumar et al., 2008; Laidi and Houenou, 2016), all subjects were medication-naïve. The benefits of this approach to recruitment are discussed in the Methods Section 3.1.1. By utilising research strategies such as randomisation and experimental manipulation in combination with two fMRI techniques, we aim to overcome several of the limitations of correlational studies in drawing causal inferences about brain-based reward and penalty mechanisms in depression.



1.8.2 Hypotheses

This thesis examines three hypotheses for the effect of lurasidone on (1) neural correlates of reward and penalty processing and (2) reward and penalty-related prediction error signal and (3) cerebral blood flow in depression.

We investigate reward and penalty processing because responses to positive and negative contexts contribute mutually to depression course (Rottenberg et al., 2002). Depression is characterised by hyporeactivity to reward (Admon et al., 2015a; Forbes et al., 2009; Forbes et al., 2010; Gotlib et al., 2010a; Keren et al., 2018; Knutson et al., 2008; Luking et al., 2016c; Olino et al., 2014; Pizzagalli et al., 2009a; Rzepa et al., 2017; Segarra et al., 2016; Sharp et al., 2014) and hyperactivity to aversive stimuli (Admon et al., 2015a; Engelmann et al., 2017; Gotlib et al., 2010b; Luking et al., 2016b), and thus an antidepressant effect could be brought about by increasing reward, decreasing salience to negative events, or, both simultaneously. Given the relative paucity of literature on processing of losses (Keren et al., 2018 in press), our study is designed to interrogate both anticipation and feedback of rewards and penalties. Broadly speaking, we hypothesise a normalisation of fronto-striatal reward and/or penalty function and prediction error following acute-dose administration in depression. We anticipate that subjects scoring high on depression will show a baseline difference in fronto-striatal activity which will be reverted by acute-dose lurasidone. Moreover, we seek to address a key concern in pharmacoinaging studies, namely that shifts in global or regional CBF could underlie changes observed in BOLD fMRI signal. We therefore also use ASL, an imaging modality that allows the quantification of cerebral blood flow at rest, to disentangle global and regional CBF changes from BOLD fMRI signal. The hypotheses are described in detail below and summarised in Table 1.12.

Hypothesis 1: Neural Correlates of Reward and Penalty processing.

This study used the monetary incentive delay (MID) task in conjunction with fMRI to assess anticipatory vs. consummatory phases of reward and penalty processing (see Methods Section 3.5 for a detailed description of the task). As a result, four hypotheses were formulated for the effect of medication and depression severity on the anticipation of reward and penalties ((i) Reward Anticipation (ii) Penalty Anticipation), and the feedback of reward and penalties ((iii) Reward Outcome (iv)

Penalty Outcome). Specific predictions are outlined below and are underpinned by the following broad hypothesis: If altered neural activity during reward processing is a key mechanism for depression, then lurasidone's antidepressant effects may involve *normalising* activity in the brain's reward network. This implies a baseline difference dependent on depression severity (i.e. a significant difference in neural activation between high and low depression severity groups on placebo, which is normalised by lurasidone). Moreover, we predicted that these changes would be apparent within the first few hours of the drug dose because previous studies have shown that single-dose administration of antidepressants (Harmer, O'Sullivan, et al., 2009; Murphy, Norbury, O'Sullivan, Cowen, and Harmer, 2009) and dopamine antagonists (Admon et al., 2017; Handley et al., 2013) is sufficient to detect changes in neural activity in patients as well as healthy volunteers.

Hypothesis 1a: Reward Anticipation

With reference to the literature review on reward and penalty processing abnormalities in depression (see Section 1.5.5.1), one would expect a normalisation response to be characterised by a potentiation of striatal *reward anticipation* signals in depressed individuals. Indeed, this direction of response, albeit not statistically significant, was found using a single dose of dopamine antagonist amisulpride in depressed and healthy individuals (Admon et al., 2017). However, other studies using dopamine antagonists in healthy controls have demonstrated either no change with olanzapine (Abler et al., 2007) or blunted responses with haloperidol or higher doses of amisulpride (Pessiglione et al., 2006). Given that we used a low dose of lurasidone, and it has a more similar binding profile to SGAs olanzapine and amisulpride, than FGA haloperidol, *we hypothesised* that lurasidone will increase striatal activation during reward anticipation. In line with the results of other intervention studies (Burkhouse et al., 2016; Rice et al., 2015; Vrieze et al., 2013b; Walsh et al., 2016), we predicted that these effects will be most pronounced in individuals with higher depressive symptoms and anhedonia (i.e. more discrepant neural pattern to controls at baseline is related to greater change with intervention).

Hypothesis 1b: Penalty Anticipation

In contrast to reward anticipation, the direction of a normalisation response for *penalty-related anticipation* in depression is less clear. This is attributable to the mixed findings of the literature review with some studies showing blunted (Rzepa et al., 2017; Schiller et al., 2013; Stoy et al., 2012a; Ubl et al., 2015a) and others, increased (McCabe et al., 2009; McCabe et al., 2012) responses to penalty cues in depressed relative to healthy control subjects. Similarly, treatment studies have shown that whilst acute amisulpride administration (Admon et al., 2017) and six week escitalopram treatment (Stoy et al., 2012) significantly *increase* striatal responses to penalty cues in depressed individuals; seven day reboxetine and citalopram treatment *decrease* neural responses to aversive stimuli in OFC and insula, relative to placebo (McCabe et al., 2010). Therefore, an exploratory, non-directional hypothesis was formulated for brain regions that are commonly recruited during loss-related processing (Bartra et al., 2013; Engelmann et al., 2017; Gotlib et al., 2010a). *We hypothesised* that lurasidone will alter (increase or decrease) the penalty-related anticipation signal in ACC, anterior insula, amygdala and striatal regions and that these effects will be greatest in individuals with higher depressive symptoms.

Hypothesis 1c: Reward Outcome

A prominent finding of the literature review was the association between depression, consummatory anhedonia, and blunted striatal responses to *reward outcomes* (Admon et al., 2015a; Forbes et al., 2009; Forbes et al., 2010; Gotlib et al., 2010b; Hagele et al., 2015; Knutson et al., 2008; Pizzagalli et al., 2009a; Segarra et al., 2016; Sharp et al., 2014; Yang et al., 2016). A normalisation response would thus constitute an increase in striatal activity to positive feedback in depressed individuals. Indeed, acute amisulpride administration has been shown to significantly increase reward-related striatal activation in MDD (Admon et al., 2017). On the basis of this converging evidence, *we hypothesised* that lurasidone will increase the reward feedback signal in the ventral striatum, namely the caudate, putamen and NAcc. Moreover, it was predicted that these effects will be most pronounced in individuals with higher depressive symptoms and consummatory anhedonia.

Hypothesis 1d: Penalty Outcome

As discussed in Section 1.5.5.2, heightened sensitivity to negative outcomes in depression may be reflected by elevated loss-related signals in the ACC, anterior insula, and striatum (Admon et al., 2015a; Engelmann et al., 2017; Gotlib et al., 2010b; Luking et al., 2016b). Thus, the expected direction of a normalisation response would be to reduce activity in these regions to a level comparable of healthy control subjects. There are few studies which have investigated modulation of penalties by pharmacological compounds. However, those which have investigated this showed that acute high doses (400 mg) of amisulpride reduce aversive PEs in the striatum (Jocham et al., 2014), and low doses show a (non-statistically significant) pattern of reducing striatal responses to *penalty outcomes* in depressed individuals, relative to placebo (Admon et al., 2017). Seven day treatment with SSRI citalopram in healthy controls *reduces* activation for aversive stimuli in the lateral OFC (McCabe et al., 2010). In line with this notion, *we hypothesised* that lurasidone will reduce the penalty-related feedback signal in the ACC, anterior insula and ventral striatum.

Hypothesis 2: Reward and Penalty-related Prediction Error Signal

This thesis addresses how lurasidone influences prediction error (PE) encoding in depression, which is of relevance since reward-related PE signals are attenuated in depression (Uhl et al., 2015a) and contribute to the severity of anhedonia (Gradin et al., 2011). The effect of dopamine antagonists on the neural correlates of reward *and* penalty prediction error in *depression* has not been previously investigated; hence this part of the study was largely exploratory. The modulation of striatal PE signals is strongly associated with behavioural learning and improvement of future decisions (Pessiglione et al., 2006), both of which are essential features in the context of psychotherapy. PE trumps reward magnitude as a parameter of decision making and influences subjective mood fluctuations (Rutledge et al., 2014) over and above expected or received reward. This makes the PE a potentially important treatment parameter.

To assess the effects of lurasidone on reward and penalty-related PE, an approach that emphasises the prediction error framework was used, as has been done previously for

the MID task (Graf et al., 2016; Staudinger et al., 2009). As discussed in Section 1.4.3 and 1.5.5.3, reward-related PEs are predominantly encoded in the ventral striatum, caudate, putamen, OFC and ACC (Gradin et al., 2011; Kumar et al., 2008; Rothkirch et al., 2017; Ubl et al., 2015a). Loss-related PE signals are principally encoded in the ventral striatum, insula, ACC, thalamus and amygdala (Garrison et al., 2013; Pessiglione et al., 2006; Yacubian et al., 2006).

Hypothesis 2a: Reward-related Prediction Error

The majority of studies in the literature review demonstrated reduced encoding of *reward-related PE* in several regions of the fronto-striatal-limbic reward circuit in depression; with the degree of signal reduction correlating with syndrome and anhedonia severity (Gradin et al., 2011; Kumar et al., 2008; Rothkirch et al., 2017; Ubl et al., 2015a). Acute pharmacologically induced dopaminergic enhancements increase reward-related striatal activity and improve reward learning relative to placebo (Chowdhury et al., 2013a; Jocham et al., 2011; Pessiglione et al., 2006). If the low dose of lurasidone used in this study transiently increases dopamine release via autoreceptor blockade⁵ (Admon et al., 2017; Schoemaker et al., 1997), we can expect that lurasidone will increase prediction error signal for reward in regions of the brain's reward network (ACC, OFC, amygdala, VS), and that these effects would be greatest in individuals with more severe depressive symptoms. However, if lurasidone's D₂ antagonism reduces dopamine availability then we can expect the opposite pattern, as has been found with high doses of amisulpride (Jocham et al., 2014) and haloperidol (Pessiglione et al., 2006). Therefore, an exploratory, non-directional hypothesis was formulated and *we hypothesised* that lurasidone will alter (increase or decrease) the

⁵ We do not know unequivocally how lurasidone affects the different components of dopaminergic function in humans, for example with regard to tonic versus phasic firing, or D₁ versus D₂ receptors. Therefore, although we predict that lurasidone will modify PE-related fronto-striatal responses at the systems-level, we have to be cautious about inferring the precise mechanism at a cellular level.

reward-related PE signal in the striatum, ACC and OFC and that these effects will be greatest in individuals with higher depressive symptoms.

Hypothesis 2b: Penalty-related Prediction Error

In contrast to reward-related PE, the direction of a normalisation response for *penalty-related PE* in depression is less clear. This is attributable to the relative paucity of research linking penalty-related PEs to depression/pharmacological interventions and the mixed findings of the studies reviewed. Whilst there is some evidence of enhanced encoding of penalty-related PE in the ventral striatum in depression relative to healthy volunteers (Ubl et al., 2015), there is also evidence of no group differences in penalty-related PE encoding in the striatum and insula (Rothkirch et al., 2017). Unlike reward-related PE, acute pharmacologically induced dopaminergic enhancements and administration of dopamine antagonist, haloperidol, have not had a significant effect on loss-related PE encoding (Pessiglione et al., 2006). Whilst acute dose (400 mg) amisulpride reduces aversive PEs (Jocham et al., 2014), longer term (2 week) exposure to SSRI citalopram enhances aversive PE signals in the ventromedial prefrontal cortex and ACC relative to placebo treatment (Scholl et al., 2017). In response to the limited literature, an exploratory, non-directional hypothesis was formulated for brain regions that are commonly recruited during loss-related PE processing. *We hypothesised* that lurasidone will alter the penalty-related PE signal in ACC, insula, amygdala and striatal regions and that these effects will be greatest in individuals with higher depressive symptoms.

Hypothesis 3: Sensitivity Analyses

The aim of the final hypothesis was to test the sensitivity or ‘fine-tune’ the predicted outcomes of hypotheses (1) and (2).

First, *we hypothesised* that lurasidone’s effects on reward and penalty processing in depression would not be confounded by comorbid anxiety symptoms (continuous measures of anxiety (total score on the anxiety subscale of the Hospital Anxiety and Depression Scale (Zigmond and Snaith, 1983)). This prediction was formulated on the basis of neuroimaging evidence that reward alterations are present in anxiety, albeit in an opposite direction to the alterations seen in depression (Bar-Haim et al., 2007; Forbes et al., 2009; Forbes et al., 2006; Guyer et al., 2012; Guyer et al., 2006;

Helfinstein et al., 2011; Pizzagalli et al., 2005). Therefore, we predicted that co-varying for anxiety will not impact upon lurasidone's effect on reward/penalty processing in depressed individuals.

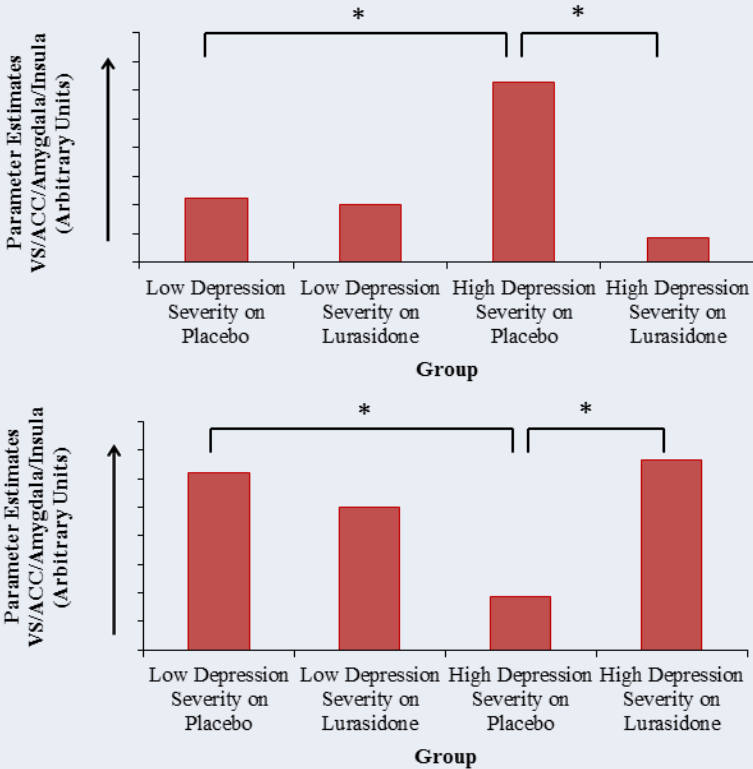
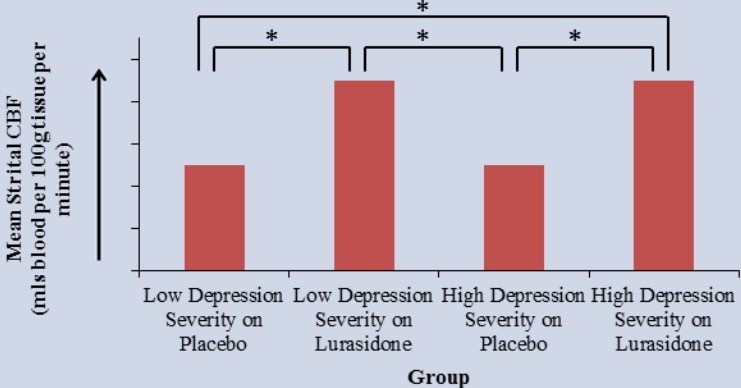
Second, *we predicted* that sedation scores, as indexed by a Visual Analogue Scale (Herbert et al., 1976), would not significantly increase following lurasidone administration and would not impact upon the relationship between medication, depression and the neural correlates of reward/penalty processing. In other words, we predicted that any effects of a low, single dose of lurasidone (20 mg) on behavioural and neural responses to rewards or penalties would not be secondary to an alteration in somnolence, alertness or tranquillity. This hypothesis was informed by evidence that lurasidone (80 mg) reduces day-time sleepiness to a similar level as a placebo-treated group and evidence that lurasidone has milder somnolence side-effects when compared to other atypical antipsychotic medications (e.g. quetiapine) over a six-week period (Citrome et al., 2014; Loebel et al., 2014c).

Third, previous studies have shown that dopamine antagonists (FGA and SGAs) potentially increase striatal cerebral blood flow at rest (Goozee et al., 2014; Handley et al., 2013; Lahti et al., 2003; Lahti et al., 2005). Increases in blood flow following antipsychotic administration may be related to increased neuronal metabolism in striatal areas due to the large density of D₂ receptors (Goozee et al., 2014). Blockade of D₂ receptors in the striatum may potentially result in disinhibition of D₂ receptor-containing medium spiny neurons and increased dopamine signalling (Fernandez-Seara et al., 2011). On the basis of these findings, *we hypothesised* that lurasidone would increase striatal cerebral blood flow in all participants relative to placebo. In addition, *we predicted* that the fMRI BOLD analyses (Hypotheses 1 and 2) would remain unchanged when controlling for the predicted increases in regional and global cerebral blood flow (CBF) under lurasidone at baseline. Controlling for global and regional CBF changes in the analysis of BOLD fMRI data represent an important step towards identifying if the effects of the drug administered are indeed neuronal. In this study, quantitative measures of baseline CBF were measured using Arterial Spin Labelling (ASL) before the participants completed the reward task.

Table 1.12. A summary of the three hypotheses tested in this thesis for the effect of lurasidone on (1) neural correlates of reward and penalty processing, (2) reward and penalty-related prediction error signal in depression and (3) cerebral blood flow. For hypotheses 1a-2b, we predict a baseline difference dependent on depression severity (i.e. significant difference in ROI activation between high and low depression severity on placebo, which is normalised by lurasidone).

Hypothesis	Predicted pattern of response based on the literature
1a. Reward Anticipation Lurasidone will increase striatal activation during reward anticipation and these effects will be most pronounced in individuals with higher depressive symptoms and anticipatory anhedonia.	<p>Striatal Activation (Arbitrary Units)</p> <p>Group</p> <p>Low Depression Severity on Placebo, Low Depression Severity on Lurasidone, High Depression Severity on Placebo, High Depression Severity on Lurasidone</p>
1b. Penalty Anticipation Lurasidone will alter the penalty-related anticipation signal in ACC, anterior insula, amygdala and striatal regions and these effects will be greatest in individuals with higher depressive symptoms.	<p>VS/ACC/Insula Activation (Arbitrary Units)</p> <p>Group</p> <p>Low Depression Severity on Placebo, Low Depression Severity on Lurasidone, High Depression Severity on Placebo, High Depression Severity on Lurasidone</p> <p>VS/ACC/Insula Activation (Arbitrary Units)</p> <p>Group</p> <p>Low Depression Severity on Placebo, Low Depression Severity on Lurasidone, High Depression Severity on Placebo, High Depression Severity on Lurasidone</p>

Hypothesis	Predicted pattern of response based on the literature
<p>1c. Reward Outcome</p> <p>Lurasidone will increase the reward feedback signal in the ventral striatum, namely the caudate, putamen and NAcc. These effects will be most pronounced in individuals with higher depressive symptoms and consummatory anhedonia.</p>	<p>VS/ACC/Insula Activation (Arbitrary Units)</p> <p>Group</p> <p>Low Depression Severity on Placebo, Low Depression Severity on Lurasidone, High Depression Severity on Placebo, High Depression Severity on Lurasidone</p>
<p>1d. Penalty Outcome</p> <p>Lurasidone will reduce the penalty-related feedback signal in the VS, ACC and insula. These effects will be most pronounced in individuals with higher depressive symptoms.</p>	<p>VS/ACC/Insula Activation (Arbitrary Units)</p> <p>Group</p> <p>Low Depression Severity on Placebo, Low Depression Severity on Lurasidone, High Depression Severity on Placebo, High Depression Severity on Lurasidone</p>
<p>2a. Reward-related Prediction Error</p> <p>Lurasidone will alter (increase or decrease) the reward-related PE signal in frontal, striatal and limbic regions: VS, OFC, ACC. These effects will be most pronounced in individuals with higher depressive symptoms.</p>	<p>Parameter Estimates VS/ACC/OFC (Arbitrary Units)</p> <p>Group</p> <p>Low Depression Severity on Placebo, Low Depression Severity on Lurasidone, High Depression Severity on Placebo, High Depression Severity on Lurasidone</p>

Hypothesis	Predicted pattern of response based on the literature
<p>2b. Penalty-related Prediction Error</p> <p>Lurasidone will alter the penalty-related PE signal in ACC, insula, amygdala and striatal regions and that these effects will be greatest in individuals with higher depressive symptoms.</p>	 <p>Parameter Estimates VS/ACC/Amygdala/Insula (Arbitrary Units)</p> <p>Group</p> <p>Low Depression Severity on Placebo, Low Depression Severity on Lurasidone, High Depression Severity on Placebo, High Depression Severity on Lurasidone</p> <p>Parameter Estimates VS/ACC/Amygdala/Insula (Arbitrary Units)</p> <p>Group</p> <p>Low Depression Severity on Placebo, Low Depression Severity on Lurasidone, High Depression Severity on Placebo, High Depression Severity on Lurasidone</p>
<p>3c. Cerebral Blood Flow</p> <p>Lurasidone will increase striatal cerebral blood flow in all participants relative to placebo.</p>	 <p>Mean Striatal CBF (mls blood per 100gtissue per minute)</p> <p>Group</p> <p>Low Depression Severity on Placebo, Low Depression Severity on Lurasidone, High Depression Severity on Placebo, High Depression Severity on Lurasidone</p>

Chapter 2 - Imaging Methods

There are a basic set of principles which underlie the success of magnetic resonance imaging (MRI). In this section, I give an overview of these essential facts to provide an understanding of how this technique is applied to imaging the brain. Different function MRI (fMRI) methods, including Blood-oxygen-Level-Dependent (BOLD) and Arterial Spin Labelling (ASL) imaging will be summarised as well as a description of how these are used in conjunction with cognitive tasks and pharmacological administration.

2.1 Magnetic resonance imaging

2.1.1 Principles of MRI

Hydrogen is the third most abundant element in the human body, thereby making it a useful marker for medical imaging. MRI relies on the way that the components of the hydrogen nuclei (protons) in water react to the magnetic field created by a superconductive magnet. In other words, the signal in MRI comes from the magnetisation of hydrogen protons in the body. Each proton has a small magnetic moment, or 'spin' and when a non-external magnetic field is present the magnetic dipole moments are randomly oriented. However, in the main magnetic field of the scanner, named B_0 , the net magnetisation of the spins aligns with B_0 which defines the direction of the positive z-axis. At this stage the protons are in a relatively organised, low energy state.

Energy generated by a radiotransmitter, referred to as a radiofrequency pulse, excites the spin system and leads the net magnetisation to move into the transverse plane (see Figure 2.1). Thus, the protons shift into a high energy state and this excitation pulse also brings the spins into phase, resulting in a strong net magnetisation in the transverse plane, which is what induces the signal. Once the radiofrequency pulse is discontinued, excitation stops and the hydrogen nuclei relax (return) to their original state. Specifically, two types of relaxation occur: the net magnetisation returns to the

z-axis (T1 relaxation) and the spins dephase causing the net transverse magnetisation to decrease (T2 relaxation) (see Figure 2.1) (McRobbie et al., 2006).

This change in magnetisation is called the “Free Induction Decay” and comprises the MR signal, which can be detected by radiofrequency coils tuned to the Larmor Frequency. Differences in the amount of signal from different tissues is what leads to contrast. Tissues such as white matter (WM), grey matter (GM) and cerebrospinal fluid (CSF) each have different intensity curves for T1 and T2 relaxation and these curves are characterised by the time constants, T1 and T2, (i.e. the time it takes for 63% of the magnetisation to recover or decay) (Westbrook, 2009). For example, as CSF is formed mostly of water, it has the highest concentration of hydrogen and thus more spins contributing to the net magnetisation (Blink, 2004). The location of the signal can be determined by modulating the local magnetic field (and therefore the resonant frequency of the hydrogen nuclei) by applying magnetic field gradients. These vary linearly along three orthogonal planes (x, y and z axes) and are frequently referred to as the slice-selection, frequency encoding and phase encoding gradients. The order of magnetic gradient superpositions and the radiofrequency pulses used to create MR images is called the pulse sequence. Structural MRI images are created by reconstructing the signal obtained from the water molecules in the brain into an image. This is done using a mathematical process called a Fast Fourier Transform. The MRI signal is spatially organised into three-dimensional units known as voxels (i.e. cubic pixels).

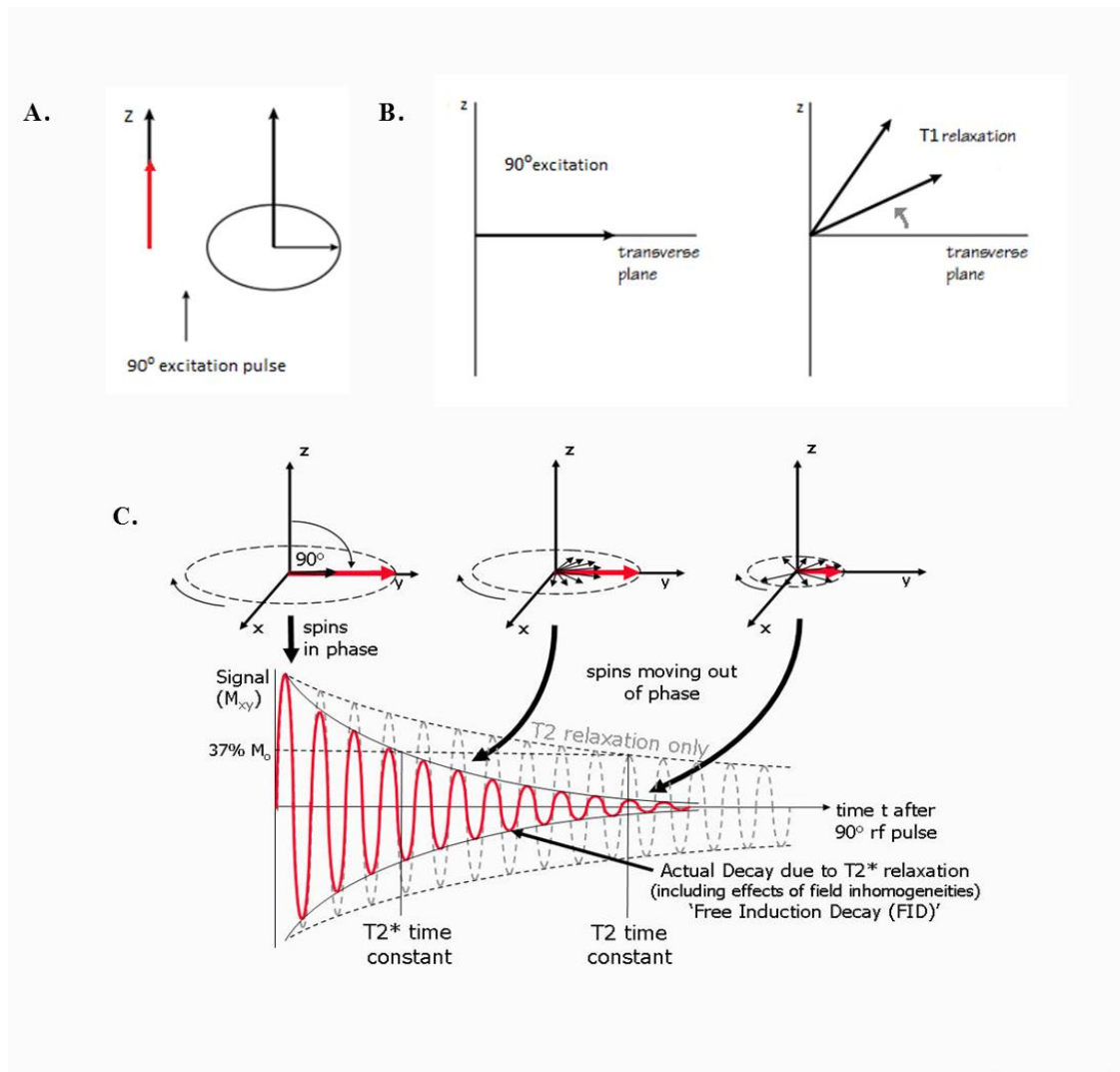


Figure 2.1. A. Excitation. Adapted from Westbrook (2009). B. T1 relaxation. Adapted from Westbrook (2009). C. T2 relaxation. Adapted from Ridgway (2010) with permission.

2.1.2 Principles of fMRI

Brain activity can be defined as the signalling activity of neurons (ie. action potential spiking) and the integrative activity between neurons. However this is difficult to measure directly and non-invasively. Thus blood-oxygen-level-dependent (BOLD) contrast in functional magnetic resonance imaging (fMRI) is used to draw conclusions about brain activity in response to manipulations of sensory, cognitive and behavioural conditions. The basic assumption being that brain activity is linked to metabolic activity in the brain and indicated by changes in blood oxygen. Specifically, the

haemodynamic response (HDR), (i.e. the increase in oxygen-rich blood delivery to active brain areas) underlies the BOLD contrast, and the magnetic properties of oxyhaemoglobin and deoxyhaemoglobin increase and decrease the MR signal respectively (Thulborn et al., 1982). In this next section, I outline BOLD signal generation in greater detail, followed by a discussion of whether BOLD contrast correlates with neural activity; is as a result of energy consumption; is unified across brain areas and individuals and applications of BOLD fMRI. Indeed, as BOLD fMRI is the neuroimaging method used in this thesis, it is important to understand the underlying assumptions of this signal generation and its limits.

2.1.2.1 *HDR and BOLD contrast*

The HDR is the main assumption for why BOLD contrast is often taken as a surrogate of brain activity. It is firstly important to understand how the HDR affects BOLD contrast. BOLD contrast is not a quantitative measure and its amplitude depends on the mismatch between cerebral blood flow (CBF), cerebral blood volume (CBV), blood oxygen supply and oxygen and glucose metabolism. Whilst oxyhaemoglobin in red blood cells is diamagnetic, deoxyhaemoglobin is paramagnetic due to its unpaired electrons (Ogawa et al., 1990; Pauling, 1936). The latter reduces T2* dephasing time and BOLD signal (Figure 2.2) in gradient echo images (Thulborn et al, 1982). When cerebral blood flow (CBF) increases, somewhat counter intuitively, neuronal activity decreases the concentration of deoxyhaemoglobin in the venous space (Figure 2.2) thereby increasing BOLD signal intensity by 1-3%.

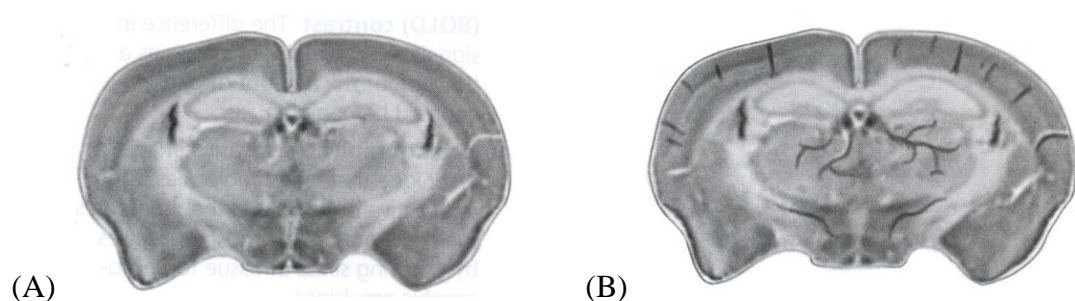


Figure 2.2. Rats breathing (A) 100% oxygen versus rats breathing (B) 21% oxygen (normal air) to manipulate blood oxygen level. Rats breathing normal air have less signal along the blood vessels in the cortex, indicating increased levels of deoxygenated haemoglobin (Ogawa et al., 1990). Adapted from Heuttel et al., (2009) with permission.

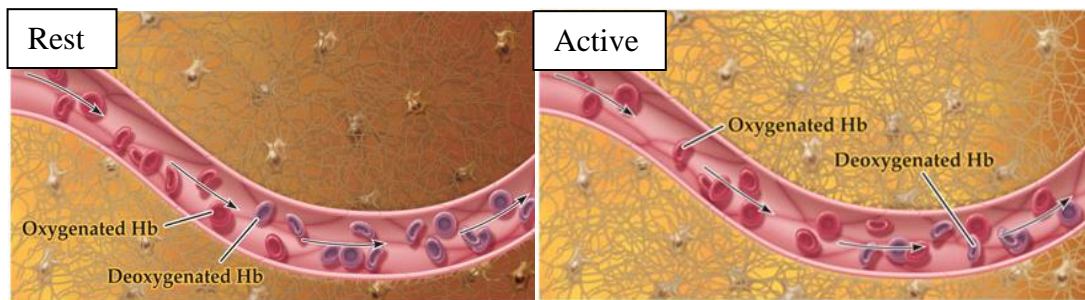


Figure 2.3. Illustration that when neurons are active there is a decrease in the ratio of deoxyhaemoglobin to oxyhaemoglobin. Adapted from Huettel et al., (2009) with permission.

The underlying features of the HDR must be evaluated in order to understand whether the relation between the BOLD signal and the underlying neural activity is qualified.

2.1.2.2 ***Does an increase in CBF, and thus BOLD contrast, correlate with neural activity?***

The first assumption to be addressed is whether neural activity contributes to the generation of the HDR and thus BOLD contrast. This has been investigated by using a combination of BOLD contrast imaging and intra-cortical recordings. Despite early studies suggesting a quantitative relationship between the action potential spike rate of neurons and the HDR (Rees et al., 2000), it is now agreed that BOLD contrast is more indicative of synaptic activity (Logothetis and Pfeuffer, 2004). Logothetis et al., (2001) showed that an increase in local field potentials (LFPs) (i.e. cooperative activity between neural populations) gave a significantly better estimate of a positive BOLD signal than the increase in spiking output of neural populations. Specifically, LFPs in the visual cortex and the BOLD response remained elevated throughout the duration of a visual stimulus, whilst the spiking output of neural populations did not. Indeed, a decrease in LFPs is also correlated with a negative BOLD response, which is thought to be indicative of inhibitory signals (Boorman et al., 2010). Therefore, if the definition of brain activity encompasses both LFPs and spiking output, the BOLD contrast seems to be a relatively accurate indicator of the former brain activity event.

The limit of its accuracy is that both inhibitory and excitatory signals contribute to the BOLD contrast, whilst within a neuron these signals may cancel out (Huettel et al., 2009). Moreover, the temporal and spatial specificity of the HDR is problematic as its peak occurs approximately 4-6 seconds after stimulus onset (Chen et al., 2011) and the BOLD effect occurs in an area larger than the focus of neuronal activity (Iadecola et al., 1997). When also considering that a typical fMRI voxel (3x3x3mm) contains a vast capillary network, millions of neurons and billions of synapses (Logothetis, 2002) the power of the BOLD signal to effectively signal neural activity at the anatomical level diminishes.

Given that these limits are inherent of the HDR, they are often overlooked and a favourable view is that positive and negative BOLD signals do correlate with LFPs. The next question is whether it is accurate to assume that energy utilisation by active neurons causes an increase in CBF and BOLD signal.

2.1.2.3 ***Are CBF and BOLD signal changes directly driven by energy consumption from neural activity?***

Indeed, it was initially assumed that this was the case (Attwell and Iadecola, 2002). Due to the low stores of glycogen in the brain, energy is supplied by glucose and oxygen in the blood (Clarke and Sokoloff, 1994). Importantly, oxygen is required to break down glucose into ATP, the energy currency of neurons (Sokoloff et al., 1977). As expected, several experiments using a deoxyglucose method revealed a coupling between regional cerebral activation, CBF and glucose consumption with a correlation coefficient of $r > 0.95$ ($p < 0.001$) (Sokoloff, 1977). It was generally assumed that the HDR was driven by energy consumed in the repolarisation of the neural membrane (Jueptner and Weiller, 1995). Hoge and colleagues (1999) also demonstrated a linear correlation between CBF and oxygen consumption in activated cortical regions. However, these correlations do not signify that CBF is directly driven by energy consumption and thus oxygen delivery.

Indeed, there is evidence that CBF and energy consumption can be dissociated and can be seen as occurring in parallel with one another rather than one being a cause of the other (Attwell and Iadecola, 2002). A ‘feed-forward’ mechanism of oxygen delivery in the blood can account for the increase in CBF, and thus BOLD contrast, irrespective of falling oxygen levels from neuronal activity. It has been proposed that an

overabundance of oxygen delivery maintains an adequate oxygen tension gradient (Kassissia et al., 1995) so that oxygen readily diffuses through the endothelium of capillaries to mitochondria (Devor et al., 2011). In particular, HDRs seem to be driven by neurotransmitter-related signalling (Attwell et al., 2010). When neurons release glutamate (Fergus and Lee, 1997), neurons stimulate the synthesis of substances used in vasodilation, such as nitric oxide synthase (NOS) (Meng et al., 1995) which subsequently increase blood flow (Figure 2.4). Therefore, contrary to assumptions that CBF and BOLD contrast changes result directly from energy consumption, it seems that BOLD contrast is more indicative of synaptic activity which is correlated with but not triggered by energy consumption.

2.1.2.4 ***Are changes in blood flow only controlled by neurons?***

Astrocytes are glial cells that also modulate blood flow requirements by dilation or constriction of arterioles. The release of glutamate leads to astrocytes releasing arachidonic acid and three types of metabolite which dilate vessels (Figure 2.4). Astrocytes also release potassium ions (K⁺) (Caesar et al., 1999) for vasodilation. Moreover, Peppiatt et al., (2006) found that structures called pericytes regulate blood flow in response to changes in neural activity, whereby noradrenaline leads to pericytes contracting capillaries and glutamate leads to pericytes dilating capillaries. There are thus structures, other than neurons that control CBF. Nevertheless, the function of astrocytes and pericytes is intimately linked to neural activity.

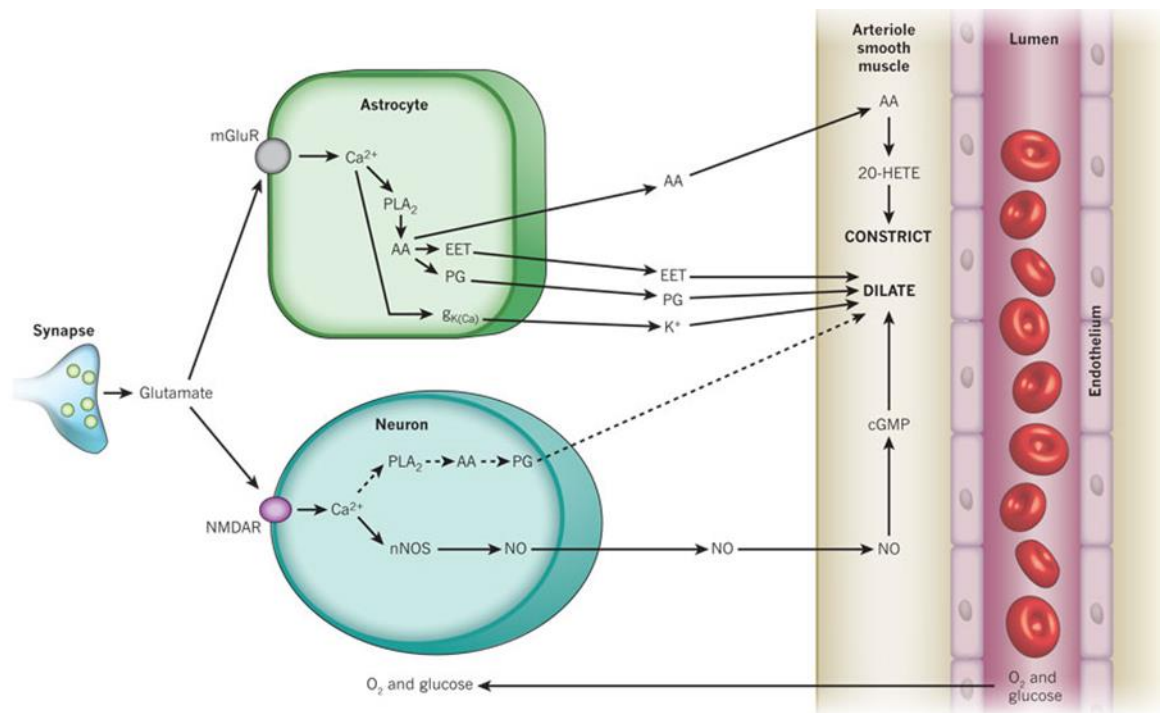


Figure 2.4. The role of astrocytes and neurons in the regulation of CBF via the release of vasodilating substances initiated by glutamate. Taken from Attwell et al., (2010) with permission.

2.1.2.5 *Can CBF, and thus BOLD signal, increase irrespective of neural activity?*

There is converging evidence that CBF-oxygen metabolism coupling is significantly lower in subcortical than cortical regions (Ances et al., 2008) and that vascular density properties change according to the function of a region (Gur et al., 2009). Variability in these physiological parameters across the brain can lead to different BOLD contrast signals irrespective of the level of brain activity. Nevertheless, BOLD response can be compared across participants for the same task and same brain region (Kim et al., 2000). Researchers must however first be aware that factors such as age, tumours and certain drugs (Rombouts et al., 2007) can change blood flow in ways unrelated to neural activity. A calibrated BOLD method, in which baseline physiological factors are taken into account, (Ances et al., 2008) and measurements of the 'Resting Brain State' (Fox and Raichle, 2007) may be able to resolve complexities in the interpretation of intersubject BOLD signals. However, both approaches have various assumptions about the cascade of physiological events occurring in the HDR that remain to be resolved (Blockley et al., 2013).

2.1.2.6 *Applications of BOLD fMRI*

Functional MRI (fMRI) has emerged as the most extensively used method in clinical research as it enables us to locate changes in cerebral activity that have been elicited either experimentally or determined by illness. Thus, the combination of in vivo structural and functional MRI has fuelled the investigation of the ‘neural correlates’ or ‘biomarkers’ of various disorders of the brain by comparing the location and degree of functional changes in patients relative to appropriate control groups or between treatment groups.

General Linear Model

Mass-univariate analysis (ie. voxel-by-voxel analysis) is a dominant method and is based on the General Linear Model (GLM). The GLM constructs a statistical model for each voxel in the brain by relating a single continuous dependent variable to one or more continuous or categorical independent variables (ie. regressors).

Inherent of the voxel-wise statistical analysis are the pre-processing steps: normalisation and smoothing. Normalisation ensures that spatial locations match to the same anatomical structures across subjects so that for each voxel in the standardised space, statistics of different groups can be completed. Moreover, as mass-univariate analysis is based on linear regressors and assumes that the underlying distributions are Gaussian, smoothing is required to make the data and residuals normally distributed, thus increasing the legitimacy of parametric tests (Lao et al., 2004). These pre-processing procedures are explained in greater detail in Methods Section 3.8.2.

Using mass-univariate analysis for fMRI data involves the construction of a first and second level GLM. It is best explained with reference to the GLM equation that can be expressed in matrix notation as follows.

$$Y = X \cdot \beta + \varepsilon \quad \text{Equation 1.}$$

The first level analysis is run separately on each subject and is used to build a model of the predicted BOLD response to the task, such that Y is the BOLD signal at various time points at a single voxel (Poldrack et al., 2011). X is the design matrix, containing the components that explain the observed data and for each voxel including: (i) BOLD timing information such as the onset (O_j^m) and duration (D_j^m) vectors (ii) the haemodynamic response function (HRF) describing the expected BOLD response shape over time and (iii) other ‘uninteresting’ regressors such as the realignment parameters for head motion (Huettel et al., 2009). The betas (β) are the parameters and define the contribution of each component of the design matrix to the observed data Y . Finally, ϵ is the error or residuals which represents the difference between the observed data, Y , and that predicted by the model, $X\beta$. Importantly, mass-univariate analysis packages such as SPM (Statistical Parametric Mapping) provide highly sophisticated methods to model the shape and magnitude of the HRF as accurately as possible.

Second level GLM combines the single subject estimates to enable group level analysis, such that Y is the activation for the task for each subject. As subjects are treated as random effects in the model, the resultant ‘random effect’ GLM is an efficient approach for making inferences about the population from which subjects were drawn.

Outputs and hypothesis testing

The output of independent statistical tests at every brain voxel is a statistical parametric map (SPM) (Friston et al., 1994) which shows regions with statistically significant differences between experimental conditions (Figure 2.5). In other words the outputted brain maps are locationist and non-connectionist signifying that they are both simple and interpretable (Brammer, 2009). SPMs of univariate statistical measures allow us to investigate (i) whether one group has a regionally higher value of a particular neuroimaging measure (such as tissue density, brain activity or blood flow) compared to another group; (ii) whether this measure correlates with an experimental variable, such as test-score or disease severity; and (iii) interactions between these effects of interest. Therefore, GLM is a flexible framework which enables the execution of different analyses including one-sample t-tests, two-sample t-

tests, paired t-tests, analysis of variance (ANOVA) and analysis of covariance (ANCOVA).

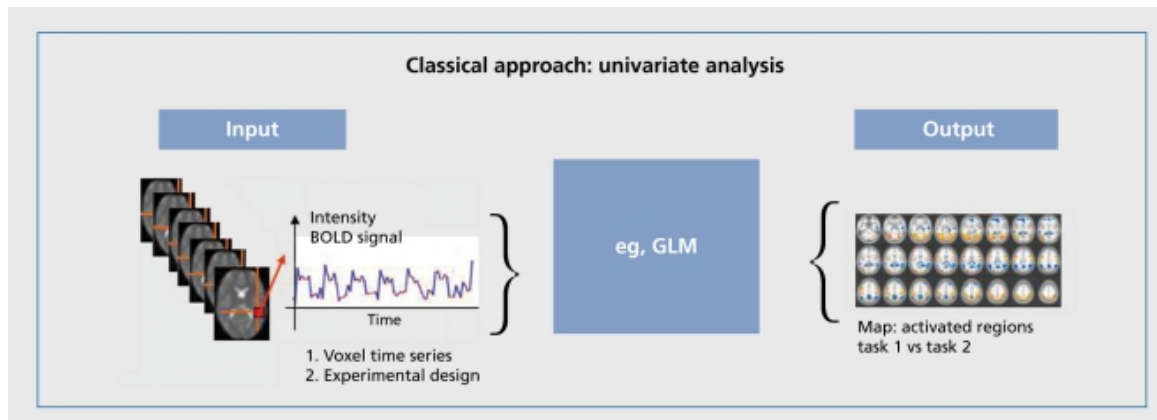


Figure 2.5. Data flow in mass-univariate analysis in an fMRI experiment with two tasks. Taken from Brammer, (2009) with permission.

Limitations of the mass-univariate analysis approach

Mass-univariate analysis has its limits. The large number of independent tests (i.e. one per voxel and a brain scan consists of 10^4 to 10^5 voxels) (Habeck et al., 2008), means that strict mechanisms, namely ‘random field theory’, are needed to correct for multiple comparisons and reduce Type I errors (Poldrack et al., 2011). This ‘curse of multiple comparisons’ renders mass-univariate analyses less sensitive to detect small changes across distributed systems (Nichols and Hayasaka 2003). Indeed, there have been replication difficulties regarding focal changes in heterogeneous psychiatric illnesses such as depression where wide-scale changes in brain structure and function are implicated. This raises a key doubt in the analysis method itself: are we correcting away true effects of interest in the data?

Furthermore, a lack of inter-voxel interaction analysis widely ignores current scientific knowledge about the connectivity and the network-like nature of brain activity in healthy and pathological circumstances (Brammer, 2009). Regions activated in one group relative to another can be expected to overlap in most regions and unlike machine learning, GLM does not have a method to integrate these statistics into an overall prediction. Thus, it cannot provide information at the subject-level, which in clinical applications, is what we are generally interested in.

Thus, an increasingly common method is to explore functional connectivity of brain regions of interest. This investigates temporal correlations in BOLD signal change across regions, either during tasks (e.g. using psychophysiological interaction analysis (PPI) to explore whether the correlation in activity in distant brain regions differs across psychological contexts; O'Reilly et al., 2012) or at rest (resting state fMRI).

fMRI versus other imaging modalities

Table 2.1 provides an overview of the general strengths and limitations of various imaging modalities. Functional MRI has superior spatial and temporal resolution compared to other prominent functional neuroimaging techniques (such as positron emission tomography [PET]) and does not require injection of radiological materials. However, as described in Section 2.1.2, there are issues concerning the temporal and spatial accuracy of images from fMRI, given the time delay in the production and subsequent measurement of deoxygenated blood and that the MR signal is more pronounced in draining veins from activated regions (due to low deoxyhaemoglobin levels). Instead, perfusion imaging, which I will describe in more detail below, may be a better localiser of neuronal activity as the signal is more specific to capillaries than BOLD. Also, BOLD is sensitive to potentially confounding signals deriving from head motion, respiration and cardiac activity.

In summary, the BOLD signal depends on the interplay between numerous physiological factors such as rates of glucose and oxygen metabolism, cerebral blood volume, cerebral blood flow and neuronal specific events. Although studies have shown that changes in BOLD signal are proportional to changes in neuronal activity, BOLD remains a surrogate measure as it relies on processes indirectly related to the underlying neurophysiology. Nevertheless, BOLD imaging has led to numerous fMRI studies that have deepened our understanding of the neural correlates of various neurocognitive functions and disorders.

Table 2.1. Characteristics of brain imaging techniques used in the study of brain function. Adapted from Apkarian et al., 2004; Kapur et al., 2006.

Method	Spatial resolution (mm)	Temporal resolution (secs)	Advantages	Disadvantages	Applications
Blood flow, and metabolic correlates of neural activity					
BOLD fMRI	3-4	3-10	Good spatial resolution, non-invasive, measures activity in cortical and sub-cortical structures, repeatable	Immobilisation, loud, stimulus-dependent technique, non-magnetic equipment, signal loss artefacts (eg. at OFC)	Localising brain activity, resting state-fMRI, effects of medication (phMRI), imaging genetics
Perfusion ASL (continuous/pulsed)	3-6		As above, quantitative measures (ml/100g/min)	As above, however without susceptibility artefacts at OFC.	Localising brain activity, resting state-fMRI, pharmacological studies
PET (FDG PET/ ¹⁵ O PET)	1.5-12	60-1000	Quantitative values with arterial sampling	Radioactivity, invasive, poor temporal resolution, limited amount of scans, expensive.	Localising brain activity
Electrical activity of neurons					
EEG/MEG	<2	0.001	Excellent temporal resolution, high patient comfort, suitable for youth	Poor spatial resolution (inverse problem), inaccurate measures of subcortical activity	Detecting temporal sequences
Single or multi-unit electrophysiology	0.01-1	0.01	Direct measure	Invasive	Detecting temporal sequences
Neurotransmitter dynamics (release, receptor binding, reuptake) and biochemical properties					

PET ^{11}C flumazenil or raclopride	1.5-12	60-1000	Measure of neurochemistry	Radioactivity, invasive, poor temporal resolution, limited amount of scans	Detecting neurochemistry
MR Spectroscopy	10	10-100	Measure of relative chemical concentrations	Immobilisation, loud	Detecting long-term changes in brain chemistry
Structural Imaging					
Structural MRI	0.2	N/A	Excellent tissue contrast	Immobilisation	Detecting long-term changes in structure
Diffusion MRI/ tractography	2	N/A	Indications of white matter tracts, integrity and connectivity	Mathematical reconstruction of fibres, limited by crossing fibres, susceptible to noise artefacts	Detecting long-term changes in connectivity
Other					
Trans-cranial magnetic/electric stimulation	10	N/A	Temporary lesions to assess causation	Poor sham/control condition, loud, risk of seizure	Investigating temporary lesions and therapeutic potential

2.1.2.7 *Arterial Spin Labelling (ASL)*

In contrast to the BOLD signal, arterial spin labelling (ASL) provides an absolute measure of perfusion (regional cerebral blood flow) and may therefore represent a physiologically specific marker of brain function.

In ASL, arterial blood is magnetically labelled using radiofrequency pulses, a process that achieves similar results to positron emission tomography (PET), but is free of ionising radiation and is entirely non-invasive. Specifically, an external radiofrequency pulse is applied in the region of the carotid arteries, in order to achieve total inversion of the arterial input to the brain. In the pulse sequence used in this study, inversion was achieved using the method known as “pseudo-continuous ASL”, introduced by Alsop (Dai et al, 2008). The “post-labelling delay” is a delay imposed to allow sufficient labelled arterial magnetisation to enter the brain volume and disperse through the arterial network to eventually reach the tissue capillaries. The delay time is made sufficiently long in order to make sure that most of the labelled spins reside only in the capillary domain. At this time, a whole brain image is acquired as fast as possible. Two, whole brain images are acquired (one with arterial blood labelling as described above) and the second non-labelled image is acquired after a double-inversion of the arterial blood in order to match the labelled scan as closely as possible without sensitivity to regional cerebral blood flow. If the labelled image is subtracted from the non-labelled one, the voxel-wise difference values are proportional to the volume of arterial blood that flows into each volume element during the post-labelling delay. This is illustrated in Figure 2.6. Arterial Spin Labelling. Protons in arterial blood are magnetically tagged by radiofrequency pulses. Labelled and non-labelling conditions are subtracted to obtain difference images, and these are averaged to create a map of intensities proportional to cerebral blood flow. Taken from Wolf and Detre (2007) with permission. Using a reference image and an appropriate mathematical model, the voxel-wise difference values are converted to a whole brain map of Cerebral Blood Flow (CBF) in traditional physiological units of ml blood/100gm tissue/min (Dai et al, 2011). The continuous pair-wise subtraction of labelled and non-labelled images exhibits minimal sensitivity to low frequency signal drift.

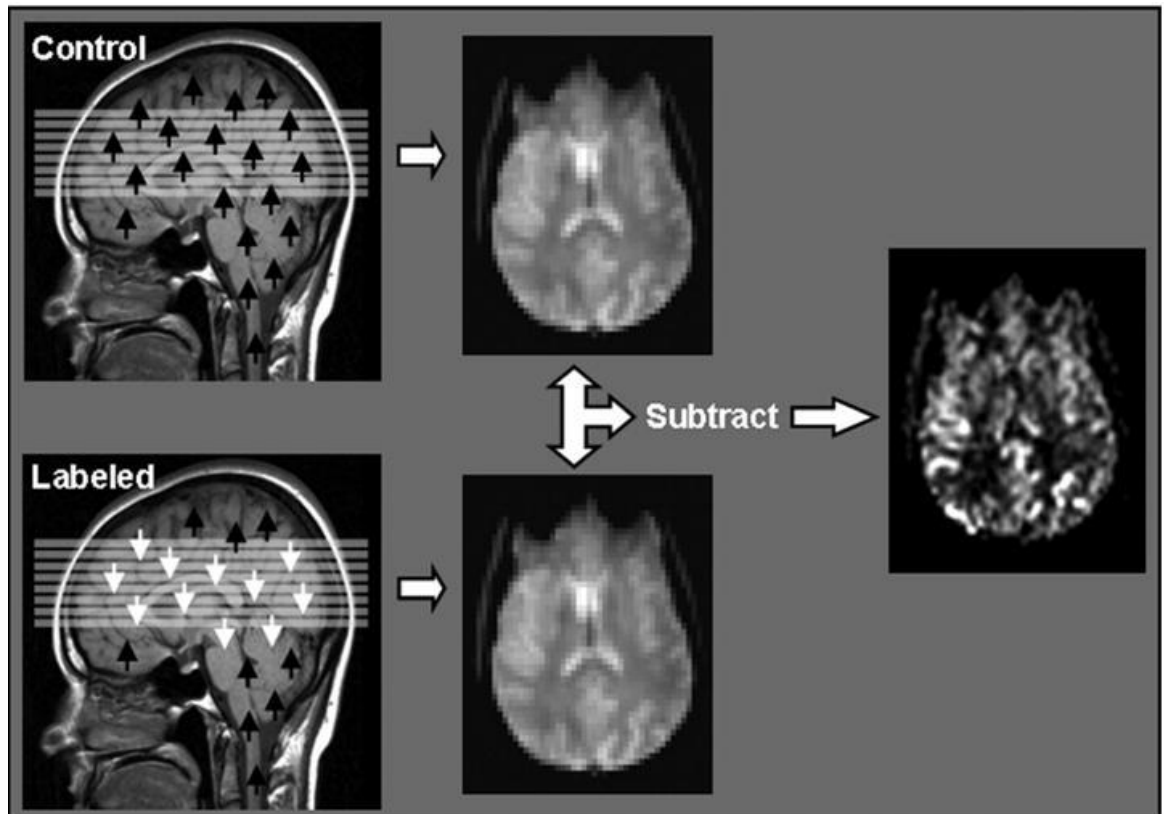


Figure 2.6. Arterial Spin Labelling. Protons in arterial blood are magnetically tagged by radiofrequency pulses. Labelled and non-labelling conditions are subtracted to obtain difference images, and these are averaged to create a map of intensities proportional to cerebral blood flow. Taken from Wolf and Detre (2007) with permission.

This thesis utilised both BOLD and ASL, as these two functional imaging modalities complement each other and therefore provide key information on neuronal activity as well as vascular coupling. A summary of the main characteristics of each method is presented in Table 2.2.

Table 2.2. Comparison between fMRI imaging techniques BOLD and ASL perfusion. Adapted from Detre and Wang, (2002).

	BOLD	ASL perfusion
Signal mechanism	Blood flow, blood volume, oxygenation consumption	Blood flow
Contrast parameter	T2*	T1
Spatial specificity	Venules and draining veins	Capillaries, arterioles
Typical signal change	0.5-5%	<1%
Imaging methods	Gradient-eco Offset spin-echo	Gradient-echo Spin-echo
Sample rate	1-3 seconds per image	3-8 seconds per perfusion image
Relative contrast-to-noise ratio	>2 with high task frequency, <0.5 with low task frequency	1
Inter-subject variability	High	Low
Imaging coverage	Whole brain	Part or most of brain cortex
Major artefacts	Susceptibility, motion, baseline drift.	Vascular artefact

Chapter 3 - Methods: Study Design and Analysis

The data included in this thesis are derived from one study which focuses on the modulatory effects of acute lurasidone administration on cerebral blood flow at rest, resting-state fMRI and task-related contexts. As the following experimental results sections contain data for cerebral blood flow and reward processing, this chapter will detail the elements of the study which are relevant for these analyses. I address general issues of methodology, subject selection, study design and procedure, with additional information given within each proceeding section as appropriate.

3.1 Participants

Forty-three participants (28 female, 15 male) were recruited from the community using the research volunteer recruitment webpage at King's College London, social media and posters at university psychological/counselling services across London.

We recruited medication-naïve subjects across the range of depression severity (Beck's Depression Inventory –II score range: 0-43), including healthy volunteers, as well as people meeting full-criteria for Major Depressive Disorder (MDD). We used this approach because symptoms of MDD are known to fall on a continuum (Angst et al., 2000; Ayuso-Mateos et al., 2010) and this allows us to assess the role of symptom level in reward processing on and off lurasidone (see Figure 4.2 and Figure 4.3 in the Results Chapter). Further justification of this continuous-sample recruitment strategy is provided in Section 3.1.1 below. Inclusion criteria restricted recruitment to right-handed individuals 18-25 years of age with no contraindications to MRI, no serious medical conditions and no lifetime substance dependence. General exclusion criteria included having a current or previously diagnosed psychiatric disorder, except depression or comorbid depression-anxiety disorder, having one or more immediate family members with a history of schizophrenia, autism or bipolar disorder, and, a history of pharmacological treatment for a psychiatric disorder or any such current treatment, contraindications to MRI (e.g., metal implants, pacemakers, claustrophobia etc.), a serious or unstable medical illness (e.g. diabetes, cardiovascular, respiratory,

endocrine, neurologic or hematologic disease), history of gastrointestinal, hepatic, or renal disease or other condition known to interfere with absorption, distribution, metabolism or excretion of medications, history of seizures, acute illness two weeks before the start of the study (screening and dosing), pregnancy, clinically significant abnormalities in Full Blood Count (FBC) and Liver Function tests (LFT), use of prescribed medication in the 3 weeks prior to enrolment or non-prescription medication (other than 1g paracetamol/24 hours) or herbal preparations in the previous seven days, receipt of another new chemical entity in the four months before dosing, or participation in another study within three months before the start of the present study, (or within one month for a non-invasive methodology study where no drugs were given), blood or needle phobia, lifetime substance dependence, being a cigarette smoker (including e-cigarettes), positive urine drug test (benzoylecgonine, d-amphetamines, d-methamphetamines, THC, morphine) and having taken illicit drugs (six months), alcohol (24 hours), caffeine (six hours), or nicotine (four hours) before scanning. To avoid craving effects, we recruited participants who were non-smokers and consumed less than three cups of coffee per day.

The flow chart illustrating the recruitment process is shown in Figure 3.1. Of the 280+ potential volunteers who responded to advertisements, 67 were invited for further screening at an assessment appointment. Of these, 44 volunteers met inclusion criteria for the study and 43 of 44 participants completed the study, thereby giving a retention rate of 97%.

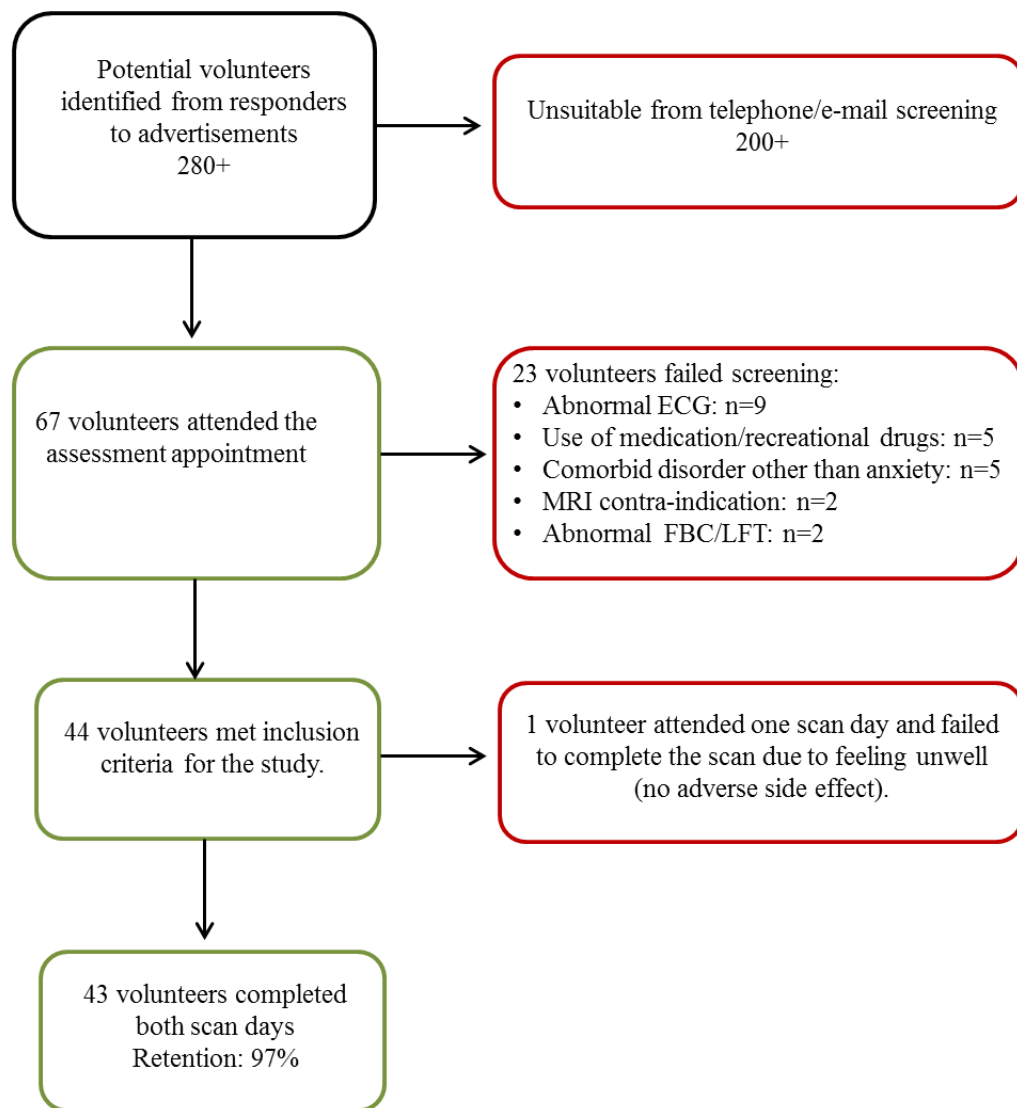


Figure 3.1. Flow chart illustrating the recruitment process.

Given that all participants completed the Mini International Neuropsychiatric Interview version 6.0.0 (M.I.N.I) (Sheehan et al., 1998), we also examined the convergence between continuous BDI-II scores and depression diagnoses as assessed by psychiatric interview (see Figure 4.2 and Figure 4.3 in the Results Chapter). Using the M.I.N.I, individuals were included in a subthreshold depression group if they self-reported having experienced, in the past two weeks, at least three depressive symptoms including at least one core symptom (abnormally depressed, irritable mood, or loss of interest) and two or more other DSM-IV depressive symptoms, without fulfilling criteria for MDD in terms of duration, symptom number, or significant

impact on functioning (Lewinsohn et al., 2000). MDD was diagnosed if the individual self-reported having experienced at least five depressive symptoms including at least one core symptom (abnormally depressed or loss of interest) most of the day, nearly every day for the past two weeks, with significant functional impairment. Comorbid simple phobia, panic and agoraphobia, social anxiety disorder and generalised anxiety disorder were allowed. MINI interview scores and diagnoses were reviewed by a consultant psychiatrist.

Participants received £230 in compensation for attending the assessment appointment and both scanning visits, in addition to their winnings from the fMRI Monetary Incentive Delay Task. All participants provided written informed consent, as approved by the Ethics Subcommittee of Psychiatry, Nursing and Midwifery Research (RESC reference number: PNM/13/14-122).

3.1.1 **Justification of recruitment strategy**

3.1.1.1 ***Spectrum of depression and anhedonia scores:***

We recruited medication-naïve subjects across the range of depression severity, including healthy volunteers, as well as people meeting full-criteria for MDD (see Figure 4.2 and Figure 4.3 in the Results chapter for depression and anhedonia symptom score distribution in the sample). This research approach is in line with the Research Domain Criteria framework (Morris and Cuthbert, 2012) (e.g. as in (Stringaris et al., 2015b) where symptom levels are related to the brain measurements). It also does justice to findings concerning the genetic underpinnings of common mental illness (Plomin et al., 2009) as well as current approaches to understanding neural system perturbation in a dimensional way (Matthews and Hampshire, 2016). This is an important consideration as common psychiatric disorders, typically conceptualised as categories, can be interpreted as lying at extremes of quantitative dimensions (Caspi et al., 2014; Plomin et al., 2009). For example, youth with subthreshold depression (sD) are known to be at very high-risk (67%) of developing major depression in adulthood (Cuijpers et al., 2005; Klein et al., 2013). A study of three large adolescent and adult community samples (n = 3003) showed that increasing levels of depressive symptoms are associated with increasing levels of psychosocial

dysfunction and psychiatric morbidity (Lewinsohn et al., 2000). Moreover, youth with subthreshold depression show comparable levels of psychiatric morbidity, functional impairment, and suicidal thoughts compared to youth with MDD (Balazs et al., 2013; Bertha and Balazs, 2013; Wesselhoeft et al., 2013). The shared phenomenology and outcomes in youth MDD and sD, although with sD being a somewhat milder version (Rapaport et al., 2002) suggest that depression may be best conceptualised as a continuum of severity (i.e. a dimensional view) (Angst et al., 2000; Ayuso-Mateos et al., 2010).

Indeed, Stringaris et al., (2016) showed that alterations in the brain's reward network operate as a mechanism across the spectrum of risk for depression in a community sample of adolescents. The results showed a graded significant decrease in ventral striatal activation during reward anticipation across healthy control, sD and MDD groups. Moreover, low ventral striatum activation was associated with anhedonia and predicted transition to depression in previously healthy adolescents at 2-year follow-up. Specifically, a 1-point decrease in standardised ventral striatum activation increased the probability of future subthreshold depression by 20% and clinical depression by 35%, even when accounting for depressive symptoms at baseline.

In summary, by recruiting young people across the spectrum of depression scores we can relate dimensional changes in reward-related neural activity during lurasidone administration to depression severity.

3.1.1.2 ***Medication-naïve volunteers:***

Recruiting medication-naïve volunteers allows us to test for effects associated with depression unconfounded by the effects of medication. In neuroimaging studies with medicated patients, it is unclear to what extent the medication status might have had an impact on reported blunting of reward-related neural activity in depression. As reviewed in Section 1.6.3.7, antidepressant drugs targeting serotonergic, adrenergic and dopaminergic systems can lead to alterations in resting blood flow as well as neurocognitive mechanisms. For example, there is evidence that selective serotonin reuptake inhibitors (SSRIs) reduce striatal and anterior insula responses to motivational and affective information (Kumar et al., 2008; McCabe et al., 2010) and

impact learning from feedback (Herzallah et al., 2013). Several studies report diminished striatal reward- or prediction error-related activations following administration of antipsychotic medications compared to placebo (Abler et al., 2007; Menon et al., 2007b; Pessiglione et al., 2006), or in medicated versus un-medicated patients (Worbe et al., 2011). Moreover, recent meta-analytic evidence demonstrates that long-term antipsychotic treatment contributes to structural brain changes (Fusar-Poli et al., 2013; Vita et al., 2015). Thus, the inclusion of medication-naïve participants avoids the confounding effects of both acute and chronic medication exposure on neural responses to reward and the brain structures that support reward function.

3.2 Self-report Questionnaires

3.2.1 Questionnaires measuring Depression Severity, Anhedonia and Anxiety

Depression and anhedonia scores were assessed using the Beck Depression Inventory II (Beck et al., 1996), the Snaith-Hamilton Pleasure Scale (SHAPS) (Snaith et al., 1995) and the Dimensional Anhedonia Rating Scale (DARS) (Rizvi et al., 2015) respectively. These are shown in Appendix B.

The BDI-II is a 21-question multiple-choice self-report inventory. Respondents use a four-point Likert scale to indicate how far each item applies to their experiences in the past week. The range of possible scores is 0–63 (Beck et al., 1961). The instrument has robust psychometric properties and is one of the one of the most widely used psychometric tests for measuring the severity of depression among both adults and adolescents in depression research (Wang and Gorenstein, 2013).

The SHAPS is considered the gold-standard for assessing self-report measures of anhedonia in clinical research (Rizvi et al., 2016). Several studies have shown that it is highly reliable in terms of internal consistency and test-retest stability (Franken et al., 2007; Leventhal et al., 2006; Nakonezny et al., 2015). For a scale to effectively evaluate a construct (construct validity), it should not be related to other overlapping but different constructs, such as mood and irritability-related items and anxiety in the

context of MDD (i.e. divergent validity), whilst retaining a correlation with similar constructs (i.e. convergent validity) (Campbell and Fiske, 1959). The SHAPS demonstrates good convergent and discriminant validity because it correlates with depression severity and functioning, but does not correlate with measures of anxiety (Leventhal et al., 2006; Nakonezny et al., 2010; Nakonezny et al., 2015). The SHAPS is a 14-item, 4-point Likert scale (strongly disagree to strongly agree). It focuses exclusively on consummatory pleasure for both primary (e.g. food) and secondary (e.g. money) rewards across several domains (e.g. food/drink, social interactions, achievement and sensory experience) (Snaith et al., 1995). Factor analysis of the SHAPS revealed a unitary structure that primarily loaded onto hedonic capacity (Leventhal et al., 2006; Nakonezny et al., 2010; Nakonezny et al., 2015). The SHAPS questionnaire measures state anhedonia (“last two days”), which may be more beneficial in capturing information in the context of a depressive episode, as opposed to other scales which measure anhedonia “in general” (i.e. anhedonia as a personality trait) (Rizvi et al., 2015). Indeed, the SHAPS has shown the ability to measure acute changes in anhedonia (Lally et al., 2014; Martinotti et al., 2012; Willner et al., 2005).

The DARS is a ‘second-generation’ anhedonia questionnaire consisting of 17-items using a 5-point Likert scale. Unlike the SHAPS’ unitary construct, the DARS evaluates interest, motivation, effort and pleasure across four domains (hobbies, social activities, food/drink, and sensory experience). The reliability and validity of the DARS has been tested in community samples, healthy controls and MDD (Rizvi et al., 2015). The scale shows good internal consistency reliability with a Cronbach- α ranging from 0.92-0.96 for the total DARS score and 0.75-0.92 for the subscales. The DARS shows good convergent validity with the SHAPS and divergent validity with depression scores (Rizvi et al., 2015).

The DARS scale has four main advantages or additions when compared to the SHAPS scale. First, it has a component structure based on reward type, (hobbies, social activities, food/drink, and sensory experience). It may therefore be useful for determining whether deficits in reward processing are dependent on one reward type, over and above another. Second, the scale was designed to increase scale generalisability while maintaining specificity. Respondents provide their own examples of rewarding experiences (generalisability) across the four domains (retaining item specificity). By tapping into the subjective nature of what respondents

find rewarding, the scale may also function to capture events or activities that elicit stronger hedonic responses. Third, it evaluates different facets of reward processing (interest, motivation, effort, and enjoyment of reward) within each domain. This is an important consideration given emerging evidence that partially dissociable neurobiological systems support different aspects of reward processing (Der-Avakian and Markou, 2012). Forth, the DARS evaluates interest in the time frame of “right now” which enables repeat testing that can aid in assessing the stability of anhedonia over time. However, it must be noted that further research is required to examine the test-retest reliability of the DARS. For the aforementioned reasons, both the SHAPS and DARS questionnaires were used to assess anhedonia in the current study.

Participants also completed additional questionnaires to assess mood, anxiety and irritability: Mood and Feelings Questionnaire (MFQ) (Angold et al., 1995), Hospital Anxiety and Depression Scale (HADS) (Zigmond and Snaith, 1983) and the Affective Reactivity Scale (ARI) (Stringaris et al., 2012).

The HADS is a fourteen item scale in which seven of the items relate to anxiety and seven relate to depression (see Appendix B). Participants responded on a 4-point Likert scale. The HADS has been utilised extensively over the last thirty years (Coyne and van Sonderen, 2012), however, a recent review showed considerable inconsistency in the latent structure of the HADS (Cosco et al., 2012). It was concluded that the HADS may not be a dependable means of differentiating anxiety and depression for the purposes of assessing the absolute or relative levels of these variables (Bjelland et al., 2002; Coyne and van Sonderen, 2012). Considering these limitations, in this study we completed a more in-depth assessment of depression and anxiety by administering the MINI.

3.2.2 Questionnaires measuring subjective effects of lurasidone.

Since lurasidone like other atypical antipsychotics, has the potential to increase sedation (Citrome et al., 2014; Loebel et al., 2014d), the possibility arises that any effects of lurasidone on behavioural/neural responses to rewards or penalties are secondary to an alteration in somnolence, alertness or tranquillity. Therefore, subjective effects of lurasidone were captured using the Visual Analogue Scale (VAS) (Herbert et al., 1976) and State-Trait Anxiety Inventory (STAI-S) (Spielberger et al., 1970), designed for rapid assessment of sedation and state anxiety respectively.

Details for this analysis can be found in Section 3.8.6. We assessed subjective effects of lurasidone at three time points (see Figure 3.3):

1. *Pre-medication*: outside the scanner, approximately 10 minutes prior to the medication administration and 180 minutes prior to the scan.
2. *Pre-scan (peak-of-medication effect)*: outside the scanner, approximately 170 minutes after medication administration and 10 minutes prior to the start of the scan.
3. *Post-scan*: outside the scanner, approximately 280 minutes after medication administration and 10 minutes following cessation of the scanning session.

Both questionnaires required respondents to indicate how they were feeling in the present moment and are shown in Appendix B. The VAS consists of 16 item scales (100mm lines) to measure mood and subjective well-being and can be summarised into two factors (Alertness and Tranquillity) (Bond et al., 1974a, b; Herbert et al., 1976). Participants were instructed to mark with a cross point on each line which corresponded best to how they were feeling at that time (e.g. from Alert-Drowsy; Calm-Excited; Lethargic-Energetic). We calculated unweighted factor scores (Factor 1 (Alertness) and Factor 2 (Tranquillity) based on the analyses of Herbert et al., (1976).

The STAI-S, which measures situational anxiety, includes 20 items and respondents indicated the intensity of the feeling on a 1 to 4 Likert scale from ‘not at all’ through ‘somewhat’, ‘moderately so’ to ‘very much so’. Both the VAS and STAI-S scales include reverse items.

3.3 Study Design and Rationale

This study was a pharmacological MRI study using a double-blind, randomised, placebo-controlled, crossover design in forty-three young volunteers (Figure 3.3). Double-blind randomised placebo-controlled designs are considered one of the most suitable designs to arrive at causal inferences (Cartwright, 1989).

Blinding: The term blinding refers to keeping participants, investigators and analysts unaware of an assigned intervention so that they cannot be influenced by that knowledge. Double-blind refers to two levels of blinding; at the level of the participant and at the level of the investigator. A participant who is unaware of which treatment is

given is less likely to have biased psychological or physical response to the intervention (e.g. favourable expectations) and more likely to comply with the study regimen (Schulz et al., 2002; Schulz and Grimes, 2002). Blinding investigators at all stages of the study (recruitment, data collection, and data analysis) makes it less likely that they will transfer their inclinations or attitudes to the participants, to differentially adjust doses, to differentially withdraw participants or be biased in their analytical methods (Nosworthy et al., 2001; Schulz and Grimes, 2002; Wolf, 1950). The goal of blinding is thus to increase objective assessment and improve the reliability of research results. I remained blind throughout data analysis and un-blinding only occurred at the stage of second-level analyses.

Randomisation: Randomisation was completed by a researcher unaffiliated with the research project. Each participant was randomly assigned to one of the two sequences of treatments. As this study was done in collaboration with the National Pharmacy at the Maudsley Hospital, the randomisation list was passed to the pharmacy for dispensing.

Placebo-controlled: To be able to comment on the effect of lurasidone on neurocognitive mechanisms, there needs to be a comparison group, and thus placebo represents the control. The placebo was ascorbic acid 50 mg tablets. Both the lurasidone pill and placebo were encased in an opaque red size 01 capsule so that both treatments looked identical across both visits.

Crossover: The crossover design has been used widely in cognitive pharmacological investigations (e.g. (Bossong et al., 2012; Doyle et al., 2013; Elliott et al., 1997b)). The crossover design signifies that each participant is randomly assigned to a sequence of treatments. The neurocognitive performance of each participant is measured twice, once following the administration of the acute drug, lurasidone, and once following the administration of a placebo. As shown in Figure 3.2, approximately half of the participants (n=22) received lurasidone on the first visit and the placebo on the second (lurasidone-placebo), and the other participants (n=21) received placebo on the first visit and lurasidone on the second visit (placebo-lurasidone). As illustrated in Figure 3.3, a one-week washout period avoids carry-over effects, and is based on the reported 18h half-life of lurasidone 40mg (Sunovion, 2013).

The crossover design has some advantages when compared to an equivalent parallel design in which subjects are randomly assigned to either a drug group or a placebo group and measures of interest are compared between the two groups. The influence of confounding covariates (i.e. non-specific individual differences such as intelligence and task engagement) is eliminated in the within-subject design as each crossover subject serves as their own control. The within-subject design affords higher statistical power than a parallel design and requires fewer subjects (Cox and Cochran, 1957). Increased statistical power stems from (i) minimising subject variance, and therefore reducing the overall random error, and (ii) increasing the drug variance. In other words, the drug variance is orthogonal to the subject variance and therefore not confounded by this. Moreover, the crossover design can uncover psychopharmacological effects of a drug which may otherwise remain undetected in a between-subjects design. For example, a drug may enhance performance on novel tasks but impair previously established performance (Elliott et al., 1997b), and reveal effects that are dependent upon baseline performance (Kimberg et al., 1997).

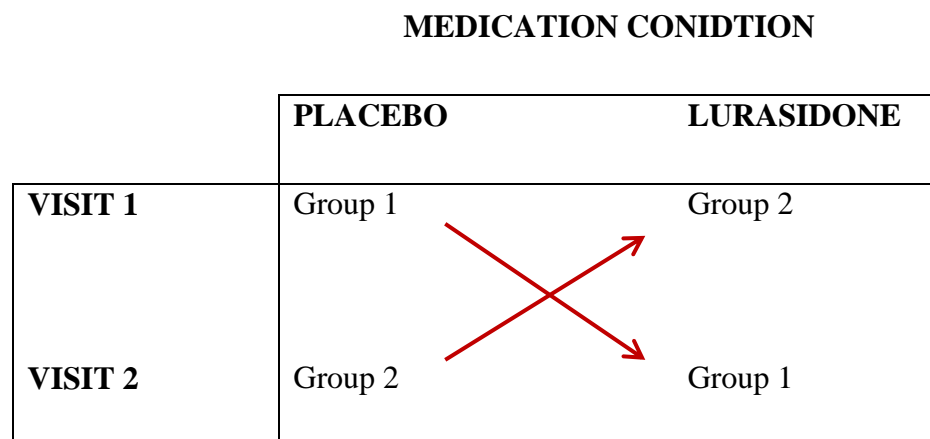


Figure 3.2. The crossover design. Participants are randomly assigned to group 1 or group 2. In this study, group 1 received placebo on the first visit and lurasidone on the second visit (placebo-lurasidone), whilst group 2 received lurasidone on the first visit and the placebo on the second (lurasidone-placebo).

Single-dose (acute) administration combined with imaging: This approach has been used successfully before (Admon et al., 2017; Handley et al., 2013; Rock et al., 2013) and avoids sedation over long periods. Acute pharmacological intervention designs, as used in this thesis, provide greater simplicity and specificity of findings, and greater

experimental control than long-term pharmaco-psychological interventions (please refer to Introduction Section 1.6.3.7 for an in-depth discussion). Acute experimental medicine studies are also more easily applicable, and less costly than the implementation of randomised control trials. Single-dose studies offer a time frame to investigate the immediate effects of pharmacological agents that target key neural mechanisms or ‘biomarkers’ in depression. Studies utilising acute-dose (Harmer et al., 2003a; Harmer et al., 2003b) and short-term treatment (Arnone et al., 2009; Godlewska et al., 2012; Murphy et al., 2009; Norbury et al., 2007) have been crucial for the development of a cognitive neuropsychological model of antidepressant drug action (Harmer et al., 2009a) (please refer to Introduction Section 1.6.2). It postulates that antidepressant drugs have early ‘bottom-up’ effects on emotional processing which become translated into improved mood and conscious appraisal over time and with exposure to a real-world environment. This study harnesses the potential of a single-dose research strategy to examine the acute effects of lurasidone on blood flow and reward processing.

Arterial Spin Labelling (ASL) and blood oxygenation level dependent (BOLD) fMRI:

The effects of lurasidone on regional cerebral blood flow (rCBF) were investigated using arterial spin labelling (ASL) and the effects of lurasidone on neural mechanisms were investigated using BOLD fMRI. Introduction Section 1.6.3.7 and Imaging Methods Section 2.1.2.7 provides an in-depth discussion of the benefits of combined ASL-BOLD imaging in pharmacological MRI (phMRI), and Imaging Methods Section 2.1.2 details the principles of each method. In brief, in phMRI, BOLD signal changes could be induced through either direct effects of the drug on neuronal activity or through non-specific effects on cerebral metabolic activity or underlying vasculature (Wise, 2006; Wise and Tracey, 2006a). ASL provides an absolute quantitative measurement of CBF, which is not confounded by changes in cerebral blood volume (CBV) or cerebral metabolic rate of oxygen (CMRO₂) (Detre et al., 2012; Detre and Wang, 2002; Detre et al., 2009). Several test-retest studies (including one ASL reproducibility study from the scanner used in this study) (Hodkinson et al., 2013) have shown that ASL perfusion measurements are highly reproducible across minutes, hours, days and weeks (Chen et al., 2010; Floyd et al., 2003; Parkes et al., 2004). These characteristics make ASL an ideal tool for phMRI for studying both intravenous and oral drug action as well as understanding drug effects on baseline

brain function (Wang et al., 2011a). Indeed, controlling for global and regional CBF changes in the analysis of BOLD fMRI data represent an important step towards identifying if the effects of the drug administered are indeed neuronal. In this study, quantitative measures of baseline CBF were measured using ASL before the participants completed the reward task. This scan order was selected to avoid carry-over effects of cognitively demanding tasks on resting blood flow (Hasson et al., 2009).

Study Timeline

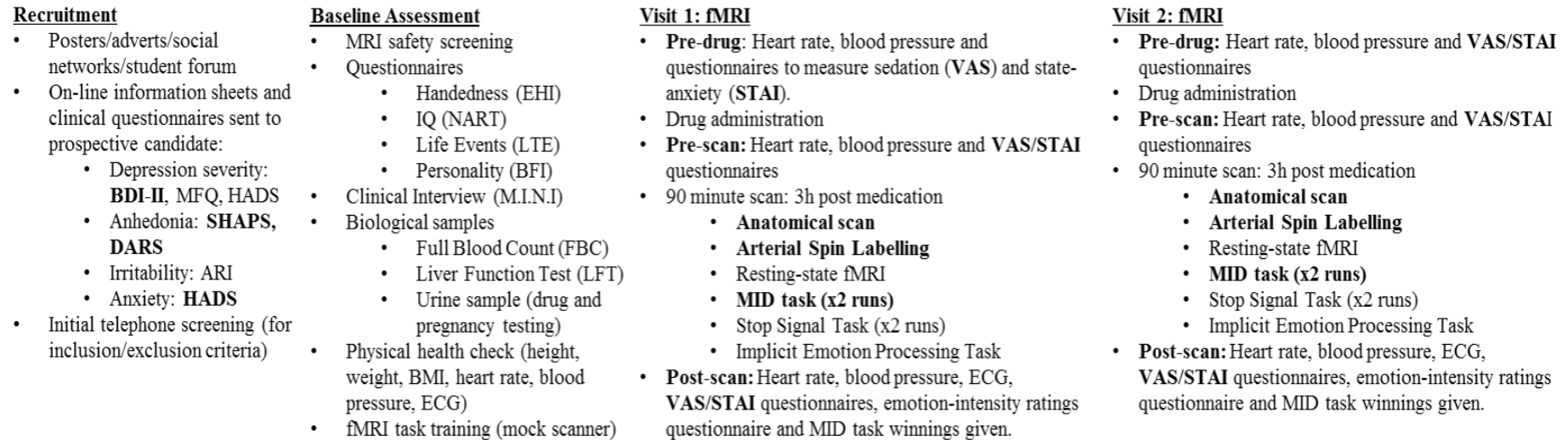
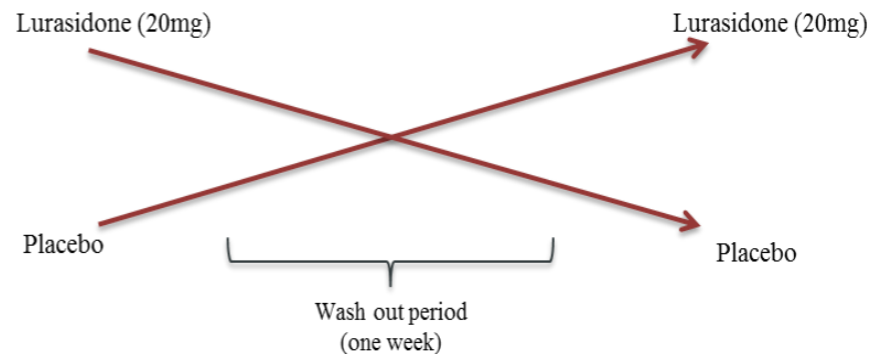


Figure 3.3. Procedure and timeline for a study investigating the effect of lurasidone on reward and penalty processing. Elements of the thesis are highlighted in **bold**.



BDI-II = Beck's Depression Inventory II (Beck, Steer, Ball, & Ranieri, 1996); **MFQ** = Mood and Feelings Questionnaire (Angold et al., 1995); **HADS** = Hospital Anxiety and Depression Scale (Zigmond & Snaith, 1983); **SHAPS** = Snaith-Hamilton Pleasure Scale (Snaith, Hamilton, Morley, Humayan, Hargreaves, & Trigwell, 1995); **DARS** = Dimensional Anhedonia Rating Scale (Rizvi et al., 2015); **ARI** = Affective Reactivity Scale (Stringaris et al., 2012); **EHI** = Edinburgh Handedness Inventory; **NART** = National Adult Reading Test (Nelson & Willison, 1991); **LTE** = The List of Threatening Experiences (Brugha et al., 1985); **BFI** = The Big Five Inventory (John & Srivastava, 1999); **M.I.N.I** = Mini International Neuropsychiatric Interview version 6.0.0 (M.I.N.I) (Sheehan et al., 1998); **VAS** = Visual Analogue Scale (Herbert, Johns, & Doré, 1976); **STAI** = State Trait Anxiety Inventory (Spielberger, Gorsuch, & Lushene, 1970).

3.4 Procedure

Figure 3.3 provides a comprehensive summary of the study procedure and timeline. Prospective candidates first completed on-line questionnaires to assess mood, irritability, anxiety and anhedonia: (Beck's Depression Inventory II (BDI-II) (Beck, Steer, Ball, and Ranieri, 1996), Hospital Anxiety and Depression Scale (HADS) (Zigmond and Snaith, 1983), Mood and Feelings Questionnaire (MFQ) (Angold et al., 1995), Affective Reactivity Scale (ARI) (Stringaris et al., 2012), Snaith-Hamilton Pleasure Scale (SHAPS) (Snaith, Hamilton, Morley, Humayan, Hargreaves, and Trigwell, 1995) and the Dimensional Anhedonia Rating Scale (DARS) (Rizvi et al., 2015)). These questionnaires were completed at the initial stages of the study in order to recruit young people from the community across a spectrum of depression and anhedonia scores. On the basis of BDI-II and SHAPS scores, prospective candidates were selected to participate in a telephone interview to briefly assess relevant psychiatric, medical and neurological history. Participants who were eligible following this screening procedure were invited to the assessment appointment (see Figure 3.1).

At the assessment appointment, participants first completed a pre-MRI safety screening. Participants then completed questionnaires to assess handedness (Edinburgh Handedness Inventory, IQ (National Adult Reading Test (Nelson and Willison, 1991), stressful life events (The List of Threatening Experiences (LTE; Brugha et al., 1985) and personality traits (The Big Five Inventory (John and Srivastava, 1999)). This was followed by the Mini International Neuropsychiatric Interview version 6.0.0 (M.I.N.I) (Sheehan et al., 1998) which assessed past and present mental health disorders. Participants' height, weight, heart rate, blood pressure and electrocardiogram (ECG, 12-lead) were measured by the experimenter and blood samples (for Full Blood Count and Liver Function Tests) were taken by a study physician. Participants also completed saliva and blood samples in the case of genotyping of 9 SNPs to cover 5-HT_{1A}, 5-HT₆ and 5-HT₇ (implicated in the mechanism of action of lurasidone) and ribonucleic acid RNA extraction. Samples were stored under the Biomedical research Centre Mental Health Biobank Project (reference number: 09/H0606/84, HTA license number: 12293). Participants provided a urine sample for drug testing and for pregnancy testing in female participants. Participants were guided through the scanning procedure in a mock scanner and

completed training for three fMRI tasks. This was done to familiarise themselves with the scanning environment and to reduce the potential for drop out. Participants practised each task for 7 minutes, which is half the amount of time of the full task length. The criteria for successful practise included rapid responding to win, loss and neutral cues of the task. Seven minutes was considered a sufficient amount of time for participants to learn that their RT responses are tracked (see Section 3.5 for task details). The assessment appointment was completed up to one month prior to the scanning sessions.

If participants fulfilled the inclusion criteria after the assessment appointment, they were invited to take part in two scan days (Figure 3.3). Participants were randomised into one of two drug administration orders: placebo-lurasidone (placebo at visit one and lurasidone at visit two), or lurasidone-placebo (lurasidone at visit one and placebo at visit two). Both scan days followed the same schedule (Figure 3.3). On arrival at the imaging centre, participants had their heart rate and blood pressure measured to ensure that they were medically fit to undergo subsequent procedures. Participants also filled in two brief questionnaires to measure sedation (Visual Analogue Scale (VAS) (Herbert et al., 1976) and state-anxiety (State Trait Anxiety Inventory (Spielberger et al., 1970)). Next, the experimenter administered a capsule of either lurasidone (20 mg) or placebo. This dose was selected to minimise post-synaptic D₂ blockade (la Fougere et al., 2005), as in similar studies of related medications (Admon et al., 2017).

Moreover, the 20 mg dose is the minimal effective dose for bipolar depression (Loebel and Citrome, 2015; Loebel et al., 2014b; Loebel et al., 2014c; Nelson et al., 2015; Suppes et al., 2016a; Suppes et al., 2016b). Given the pharmacokinetic profile of lurasidone, the pill was consumed, followed by a 350 calorie meal (Greenberg and Citrome, 2017). Peak plasma levels of lurasidone are reached at approximately 3 hours after tablet ingestion and the plasma half-life is 18hours (Sunovion, 2013). In order to align the study assessments with peak plasma levels, the MRI scan took place 3 hours after tablet consumption (Figure 3.3). Prior to the MRI scan, two hours 45 minutes after drug administration, the experimenter measured the participant's heart rate and blood pressure again, and the participant completed the VAS and STAI questionnaires. The scan lasted approximately 1.5 hours and included structural scans, Arterial Spin Labelling (ASL), Multi-echo Resting State fMRI (RS-fMRI) scan and a functional scan acquisition while completing the Monetary Incentive Delay (MID) Task, the Stop

Signal Task (SST) and an Implicit Emotion Processing Task. This thesis focuses on the fMRI analysis of ASL and the MID task. After the scan, and approximately 4.5 hours after drug administration, the experimenter assessed the participants' heart rate and blood pressure, the VAS/STAI questionnaires were completed and an ECG was collected. Participants then completed subjective ratings of the emotional intensity of face stimuli which were presented during the implicit emotion processing task in the scanner. Participants were paid in cash for their winnings from the MID task and were discharged. Thus, each scanning visit involved a stay of approximately five hours at the Centre of Neuroimaging Sciences.

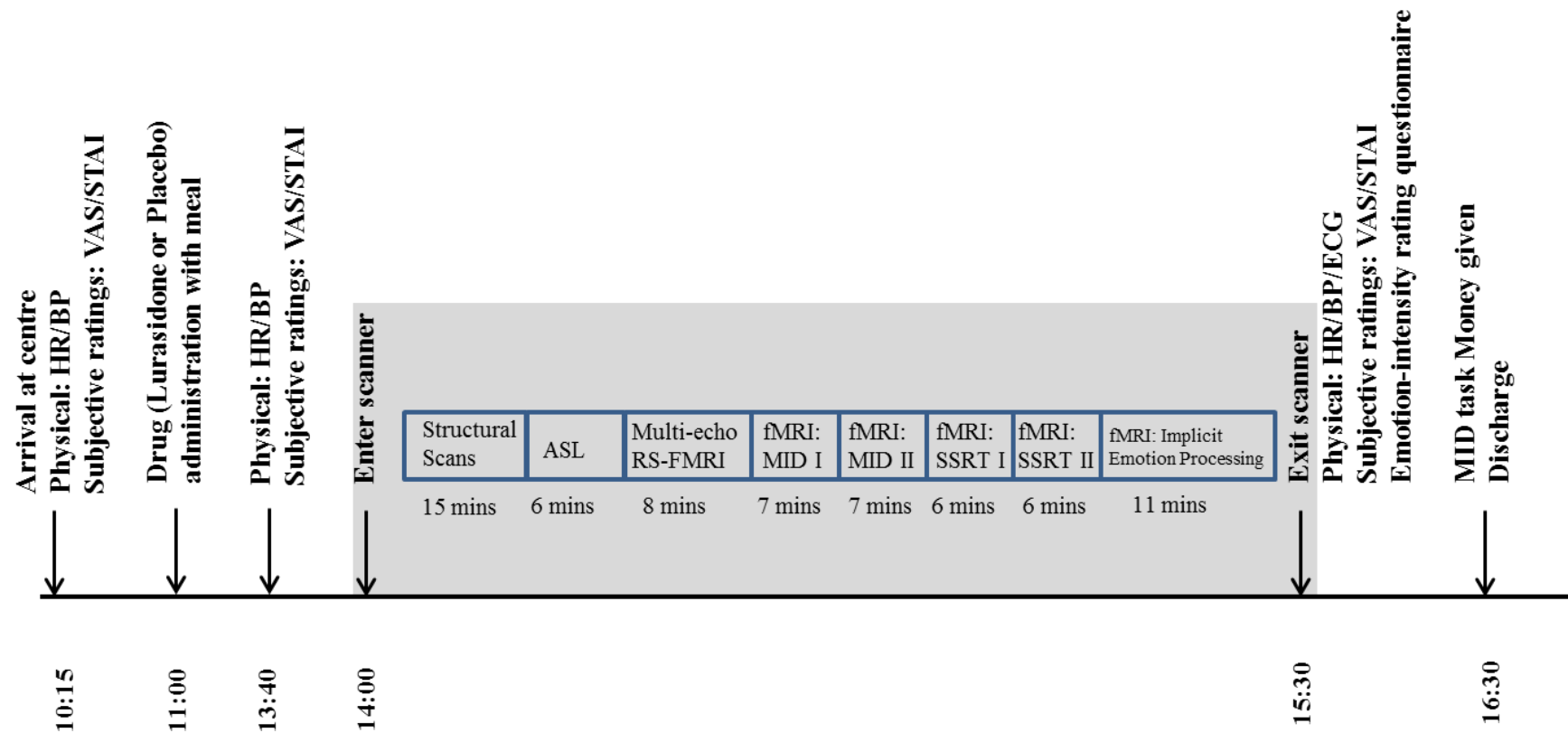


Figure 3.4. Study Day Protocol. ASL= Arterial Spin Labelling; RS-FMRI = Resting-state fMRI; MID = Monetary Incentive Delay task; SSRT = Stop Task; BP = blood pressure; HR = heart rate; ECG = Electrocardiogram; VAS = Visual Analogue Scale; STAI = State Trait Anxiety Inventory

3.5 FMRI Task: Monetary Incentive Delay (MID) task:

The Monetary Incentive Delay (MID) task used in the present study was an adaptation of the task from Knutson et al., (2001). The task can be considered as a cued reaction time test for which the symbolic cues signal the possibility of winning or losing money. Performance effects of varying incentive levels can confound the interpretation of task-related brain activations, and are minimised by emphasising the need for response speed on all trials and by using a tracking procedure that maintains performance at approximately 66% (Knutson et al., 2001). The task used in the current study had these two elements.

Each trial consisted of anticipation, response, and feedback. During the anticipation phase, participants were presented with one of three cue shapes (cue, 250 ms) denoting the type of reward that could be attained by a correct response (Figure 3.5). After a variable anticipation interval (3,800–4,150 ms), the target (white square) appeared on the centre of the screen. Participants were instructed to respond to the target as quickly as possible by pressing a button with their right index finger. Using a tracking algorithm⁶, task difficulty (i.e. the duration of the target appearance) was adapted to the performance of the subject, such that performance would be successful (reaction within the interval that the target was shown on screen) on approximately 66% of trials. The starting time the target stayed on the screen for was 400 ms and subsequently the time the target was present varied from trial to trial in 10 ms steps (150–500 ms). Responses made during the anticipation period and responses less than 100 ms were considered as "premature presses". The maximum response duration was 700 ms and reaction times greater than 700 ms were not recorded. A variable delay (blank screen) appeared after the target presentation and before feedback.

⁶ The tracking algorithm is: the number of successful trials / trials completed. If the number of successful trials is below the target ratio of 66, then 10 ms is added to the target window time of the current trial to make the trial easier. If the number of successful trials is above the target ratio of 66, it reduces the target window time of the current trial to make the trial harder.

Following the response, feedback was given (1,450 ms), indicating how much money was won or lost during the trial and the total money earned during the task. As shown in Figure 3.5, the striped circle symbol denoted a ‘win trial’. Participants received £1 for a successful response (‘win’), and £0 for an unsuccessful response (‘missed win’). The striped square symbol denoted a ‘loss trial’. Following a successful response, participants avoided losing £1 (‘avoided loss’), and lost £1 if their reaction was outside the target response window (‘loss’). The triangle symbol denoted a ‘neutral trial’ in which outcomes were not contingent on making a response within the target response window. Participants did not gain or lose money and their earnings remained £0, regardless of a successful or unsuccessful response. The screen went blank after the feedback for a variable delay (2950 ms-3300 ms) to take each trial to 9500 ms in length.

In addition to the ‘Neutral’, ‘Win’ and ‘Loss’ trials, in which a motor response was required (i.e. ‘active trials’), the task included passive trials in which no motor response was required. An ‘X’ cue was presented on screen (250 ms), followed by a blank screen (4000 ms) (trial length: 4250 ms). The rationale for including a passive condition is to pilot an alternative baseline condition to the ‘neutral cue’. Participants are presented with a symbol which requires no motor response, and it may be possible to separate out the neurocognitive processes underlying ‘the preparation of a motor response’ from ‘the anticipation of a reward’.

‘Neutral’, ‘Win’, ‘Loss’ and ‘Passive’ conditions were randomised throughout the task (13 trials each, summing up to 39 9500 ms ‘active trials’ and 13 4250 ms ‘passive trials’ in total). Task running time was 7 minutes 10 seconds. Participants completed two runs of the task at the placebo visit and the lurasidone visit to ensure that there were a sufficient number of trials (26 trials) per condition for analysis (recommended number of trials for neuroimaging analysis = 22+) (Poldrack et al., 2011) and to reduce boredom effects. Thus, four task playlists were created (two task playlists per visit), in which ‘Neutral’, ‘Win’, ‘Loss’ and ‘Passive’ conditions were randomised throughout. There was a short pause between the two runs of the task.

At the assessment appointment (first visit), participants learnt the meanings of the four symbol cues and completed a practice session of the MID task in a mock scanner for approximately 7 minutes. Participants were asked to recall the meaning of each

symbol prior to each scanning session and the need for response speed on all trials was emphasised by the experimenter. Participants received their winnings in cash at the end of the task.

Functional magnetic resonance imaging (MRI), blood oxygen-level dependent (BOLD)-responses were measured during reward anticipation and reward feedback. This study is focused on the contrasts: (i) *No-incentive Anticipation*: anticipation neutral>baseline (ii) *Reward Anticipation*: anticipation win>baseline or anticipation win>anticipation neutral (ii) *Penalty Anticipation*: anticipation loss>baseline or anticipation loss>anticipation neutral (iv) *Reward Outcome*: feedback win>missed win (v) *Penalty Outcome*: feedback loss>avoided loss.

The MID task has been extensively used and robustly activates a fronto-striatal-limbic network (see meta-analyses: Bartra et al., 2013; Diekhof et al., 2012; Kerestes et al., 2014). Plichta et al., (2012) showed that the MID task evokes robust activation in the ventral striatum with high effect sizes of VS-mean summary values (ES: 0.96-1.43) and excellent group-level activation reliability at the whole brain level and within target ROIs (intraclass correlation coefficient (ICC): 0.94). Moreover, within-subject reliability of ROI-mean amplitudes across sessions was fair to good for the MID task (ICCs = 0.56-0.62), thereby suggesting that the task is suited for within-subject designs (Plichta et al., 2012; Wu et al., 2014).

The task was programmed in Visual Studio 2008 and the images were back-projected. MRI-compatible glasses were given to participants who could not see the screen well.

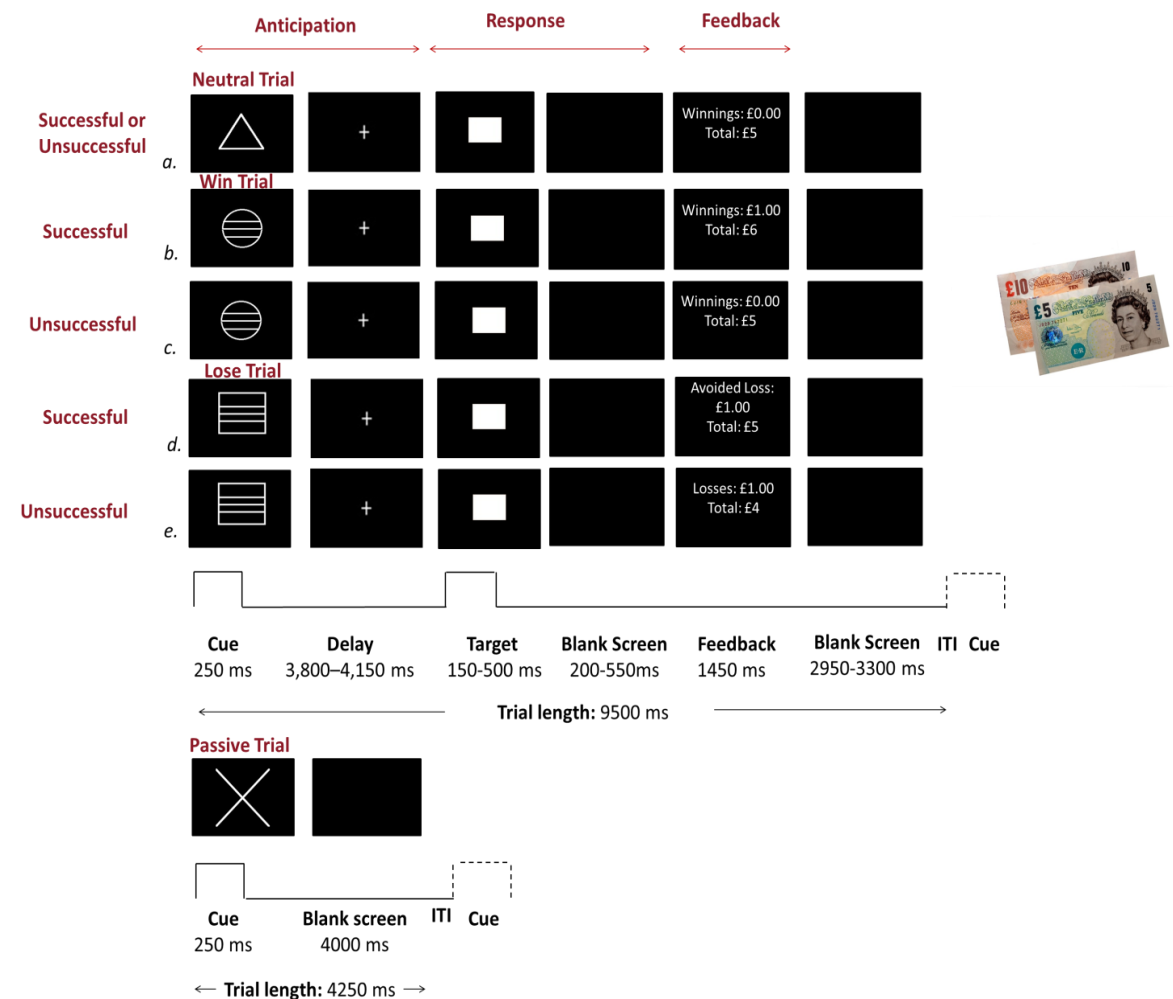


Figure 3.5. Outline of the stages and the timeline of the Monetary Incentive Delay (MID) task used during functional imaging.

3.6 Image Acquisition

Magnetic resonance data were acquired on a 3Tesla MR750 GE system (General Electric) MR scanner with a 12-channel head coil at the Centre for Neuroimaging Sciences, Institute of Psychiatry, Psychology and Neuroscience (IoPPN), King’s College London.

3.6.1 Structural image acquisition

High-resolution T1-weighted sagittal ADNI GO images were acquired [TR = 7.3ms; TE = minimum full; FOV = 270mm; matrix = 256x256mm; 1.2mm slice

thickness; 200 slices]. T2 images were acquired using FRFSE-XL forced recovery fast spin echo [TR = 4380ms; TE = 60.0ms; FOV = 240mm; matrix frequency 320, zipped to 512 phase 256; slice thickness 1.2mm with 0mm spacing; 72 slices]. The T1 and T2 images were used in pre-processing.

3.6.2 Arterial Spin Labelling

In Arterial Spin Labelling (ASL), the MR signal of water in arterial blood is selectively inverted using an external radiofrequency pulse applied in the region of the carotid arteries, in order to achieve total inversion of the arterial input to the brain. In the pulse sequence used in this study, inversion was achieved using the method known as “pseudo-continuous ASL”, introduced by Alsop (Dai et al, 2008). General principles and methods of this method are described in the Imaging Methods Chapter 2.1.2.7. In this study, labelling of arterial blood was achieved with a 1.5s long RF pulse consisting of 1500 Hanning shaped RF pulses of 500us duration, applied in the presence of a net field gradient in the direction of flow (the ‘z’ axis). A post-labelling delay of 1.5s was used, which included background suppression RF pulses to minimise the static tissue signal. Images were acquired using a 3D FSE, multi-shot ‘stack of spirals’ protocol, employing 8 spiral arms for each inter-leave and three ‘control-labelled’ averages. The images had 54 slice locations (3mm thickness, no inter-slice gap) and an in-plane resolution of 1mm after transformation to a rectangular grid (TE/TR = 11.088/4901ms, flip angle (FA) = 111°). A proton density image volume with the same parameters was acquired in order to use as a reference to compute the CBF in physiological units.

3.6.3 Functional MRI for MID Task

For each subject and at each visit, 216 whole-brain volumes (41 slices with continuous descending acquisition aligned to the AC–PC plane) were acquired using an EPI-GE sequence [Repetition Time (TR) = 2000ms, Echo Time (TE) = 30ms, flip angle = 75°, slice thickness = 3.0 mm, interslice gap = 0.3 mm and matrix size = 64x64mm].

Duration of the sequence was 7 minutes 20 seconds.

3.7 Behavioural Analysis Approach

All behavioural analyses were conducted in Statistical Package for the Social Sciences (SPSS; SPSS Inc., 2015) version 23. Initial data screening was performed in order to ensure that assumptions for parametric analyses were met. Accordingly, exploratory analysis and Shapiro-Wilk tests were completed. All behavioural data were found to be normally distributed and thus parametric tests were used.

3.7.1 MID task performance analysis

Analysing behavioural data during fMRI paradigms is vital, as it provides a context in which we can interpret the neurocognitive correlates. For example, if a HC and MDD group show similar performance on a task (as assessed by reaction time and accuracy), then it suggests that differences in neural activation between HC and MDD groups are not confounded by group differences in task difficulty.

For the MID task, we utilised the following indices to explore task performance at the lurasidone and placebo visits: (i) *Total Winnings* after completing the two task runs, (ii) *Mean Reaction Time (RT)* and (iii) *Accuracy* for the three cue types (reward, penalty and neutral cues). We completed a repeated measures ANCOVA with *Medication* (placebo or lurasidone) and *Cue Type* (Reward, Penalty, Neutral) as the within-subject variables, *Medication Order* (placebo-lurasidone, lurasidone-placebo) as the between-subject variable, and *Depression Severity* (total BDI score) as the covariate interest for (i) *Total Winnings*, (ii) *Mean Reaction Time (RT)* and (iii) *Accuracy*.

3.7.2 Subjective ratings analysis

As described in Section 3.2.2, the effects of lurasidone on sedation and state-anxiety were measured at three time points: pre-scan, peak-of-drug and post-scan utilising the VAS and STAI-S questionnaires respectively. It is important to examine subjective ratings to exclude the possibility that any effects of lurasidone on behavioural/neural responses to rewards or penalties are secondary to an alteration in somnolence, alertness or tranquillity. This analysis is described in more detail in Section 3.8.6 (alongside the other ‘sensitivity’ analyses).

3.8 FMRI Analysis Approach

The following sections will focus on the analysis techniques employed in this thesis. All analyses were applied within the framework of the Statistical Parametric Mapping (SPM, Functional Imaging Laboratory, University College London, London UK, version 12 - www.fil.ion.ucl.ac.uk/spm) and its associated toolboxes in Matlab version number: 9.1.0.441655 (R2016b) and the Statistical Package for the Social Sciences (SPSS; SPSS Inc., 2015) version 23. In order to generate statistical maps of the changes in perfusion of brain activity, the data must first go through various temporal and spatial preprocessing steps to correct for anatomical differences between subjects, or artefacts such as motion. The steps involved in preprocessing are described in the following section.

3.8.1 Pre-processing of ASL data

Spatial normalisation of the CBF maps was achieved using Automated Software for ASL Processing (ASAP; (Mato Abad et al., 2016)). This pipeline employs the Statistical Parametric Mapping suite (SPM, version 12). First, CBF maps were co-registered with a T1-weighted anatomical image after coarse alignment of the origin of both images. Unified segmentation of the T1-weighted image normalised this image to the MNI space and was used to produce a ‘brain-only’ binary mask which was multiplied by the co-registered rCBF map to produce an image free of extra-cerebral artefacts. The spatial transformation matrix was applied to the clean CBF images. CBF maps were then smoothed using an 8x8x8mm kernel.

3.8.2 Pre-processing of BOLD fMRI data

FMRI data were preprocessed and quality-assured using SPM12. This consisted of reorientation to the AC-PC line, slice timing correction, motion correction (Friston et al., 1996), multi-channel segmentation and co-registration to each participant’s structural image. The ‘normalise: estimate & write’ function within SPM12 was used, with the Montreal Neurological Institute template (MNI152). Smoothing was completed using a Gaussian kernel of 4mm Full-Width Half Maximum (FWHM). Figure 3.6 illustrates the steps of preprocessing and further description of each step is

provided below. Each preprocessing step was performed at a single-subject level, in the same manner for all participants.

Frist, *reorientation* involved setting the origin (coordinate 0,0,0 in the x,y,z axes) to the same location in each T1 and T2 structural image and the functional images. This is used as a point of reference for the preprocessing steps that follow and in this study the origin was set to the Anterior commissure/posterior commissure line.

Second, *segmentation* involves separating the structural (T1 image) into the different tissue classes using Gaussian probability distributions (created by the International Consortium for Brain Mapping) (Ashburner et al., 2014). Specifically, each voxel has an intensity value, and this has a certain probability of being in the intensity range for one of six tissue classes: grey matter, white matter, cerebrospinal fluid, bone, soft tissue and air/background. In this study we used multi-channel segmentation because the combined information from both T1 and T2 images facilitates segmentation in difficult regions (towards the top and back of the head) (Poldrack et al., 2011). To do this, the reoriented T2-weighted image was co-registered (estimate and write) to the T1-weighted image to ensure that both images had common dimensions. Then all the T1 images were put into one channel and all the T2 images into the other (in the same order) and segmentation was run.

Third, the *slice timing correction* step corrects for the temporal differences across slices that were acquired in one imaging volume (over one Repetition Time (TR)). Thus, slice timing correction allows the model to fit the data in the same way at all points (i.e. to permit the use of a single haemodynamic response function (Poldrack et al., 2011). This re-interpolates the data so that the signal at each slice is as it would have been if it had been sampled at the same time as a reference slice, typically the slice acquired halfway through one TR ($T2/2$) (Henson et al., 1999). In our study, the images were acquired using a continuous descending order of acquisition, and the middle slice was used as the reference slice. We used sinc interpolation which uses more distant data points to calculate the new value compared to linear interpolation, and therefore smooths the data less (Ashburner et al., 2014).

Forth, *realignment* (or intra-subject registration of functional images) involves aligning each image in the functional time series to each other to control for any slight movement during the fMRI scan. This utilises a six parameter rigid body

transformation, composed of the 3 translations and 3 rotations along the x,y and z axes. A least squares approach is implemented by SPM such that images are aligned by minimising the mean square error from one volume to the next. The output of the realignment is a text file for each session which is later inputted into the first-level design matrix as nuisance regressors, for that specific session and subject.

Fifth, *coregistration* is a within-subject between-modality registration step (i.e. intra-subject registration of functional and structural images). FMRI data have low spatial resolution, and thus to improve accuracy when inferring anatomical locations, the functional images are registered with the higher-resolution structural (T1-weighted) images. The co-registration was performed using non-rigid as well as rigid body transformations. As structural and functional images have different contrast, alignment is completed by maximising a quantity reflecting shared spatial information between the images, called the normalised mutual information. Indeed, the images are also smoothed slightly in order to make the cost function (mutual information) and to lessen the chance of local minima. In this step, images are aligned by minimising the mean square error from one volume to the next.

The sixth step of preprocessing is *spatial normalisation*. This step involves inter-subject registration of co-registered functional images to a standard space. In order to compare the structure or function of the brain across different individuals, the assumption of anatomical correspondence must be met. Anatomical correspondence means that a specific region in one person will be in the exact same location in the brain of another person. It is important to note that differences in the size and shape of individual's brains signify that perfect anatomical correspondence is not likely. Thus, the goal is to reduce anatomical variability and this involves each subject's high resolution structural scan (which is in 'native, unaltered space') to be warped using a combination of affine and non-linear transformations, to a 'standard space'. The standard space is a standardised atlas space or brain template with an associated coordinate system (e.g. Montreal Neurological Institute (MNI) brain). In this study, the template image was the 'spm/12/toolbox/OldNorm/EPI.nii' image with Affine regularisation to the ICBM space template (i.e. MNI) and resampling to 2x2x2 voxel dimensions. The mean resliced image was the source, so for each individual, deformations were calculated from their mean to the template and then those deformations were applied to all other images. We chose this approach as it gave

superior alignment (as assessed by visual inspection of 4D files in Mango Multi-image Analysis Software (<http://ric.uthscsa.edu/mango/mango.html>)) compared to a two-step spatial normalisation approach using DARTEL tools (Diffeomorphic Anatomical Registration using Exponentiated Lie Algebra; Ashburner, 2007).

The final step in preprocessing involves *spatial smoothing* of the images. Although this step reduces spatial resolution, it is completed for the following reasons: (i) to minimise anatomical differences between subjects following the normalisation procedures; (ii) to improve the signal-to-noise ratio (SNR) for signal which extends over larger areas by removing high frequencies; and (iii) to ensure that the data conforms to the assumptions of Gaussian Random Field theory that is used by SPM to correct for the multiple comparisons across all voxels within the brain (see Section 3.8.5) (Ashburner et al., 2014; Poldrack et al., 2011). The amount of smoothness applied, commonly between 4-12mm, is described by the full-width half maximum (FWHM). In this thesis, a FWHM of 4mm was chosen for the BOLD data as is recommended for analyses using small Regions of Interest (ROIs), such as the Nucleus Accumbens or amygdala. Please refer to Section 3.8.4.1 for further details.

3.8.3 Statistical modelling: First (single-subject) Level Analysis

Following preprocessing, single-subject data is analysed separately before being combined at the group level (Figure 3.6). As statistical analysis of the fMRI data is primarily performed at the single-voxel level, it is referred to as mass-univariate analysis. The aim is to create a map of voxels where the timeseries fluctuations follow the experimental design. This is achieved using a general linear model (GLM) approach, as described in detail in the Imaging Methods Section 2.1.2.6, and attempts to fit the observed task data to a predicted BOLD response.

3.8.3.1 First Level Model of the MID task

The anticipation, target and feedback periods are the main modelled components of the MID task and were defined as in Figure 3.5. The BOLD (Blood oxygenated level dependent) signal was modelled with a canonical hemodynamic response function that was convolved with the onset times of task regressors to compute parameter estimates

using the general linear model (GLM) at the single-subject level. The general linear model included nine task-related regressors: passive condition, three anticipation cues (neutral, win, loss) and five outcomes (with [win outcome following win cue], missed win [no-change outcome following a win cue], loss [penalty outcome following a loss cue], avoided loss [no-change outcome following a loss cue] and neutral outcome [no-change outcome following a neutral/no-incentive cue]). As there were two runs of the MID task per visit, the first-level model was set-up as four consecutive sessions, as illustrated in Figure 3.5. High-pass temporal filtering (128 second cut-off) was used to remove low-frequency artefacts and an autoregressive function (AR(1)) was used to correct for the likely autocorrelated nature of the residuals (i.e. error) following model fitting. Estimated movement parameters were added to the design matrix. These included six rigid-body movement parameters, a regressor accounting for frame-wise displacement (i.e. the 3D movement from volume 1-2,2-3 etc.), and additional binary regressors to indicate image volumes with spikes greater than 1mm, and images either side of the spike (i.e. motion scrubbing and padding). Movement analyses showed that the maximum number of volumes lost for spikes greater than 1mm was 9% (19 of 216 volumes) and all sessions were included. A repeated measures ANCOVA with two within-subject factors: *Movement* (number of spikes or total movement) and *Medication* (placebo, lurasidone) and *Depression Severity* (total BDI score) as the covariate of interest, showed that there were no significant *Medication-Movement* or *Depression Severity-by-Movement*, or *Medication-by-Depression Severity-by-Movement* interactions. Based on this analysis, no subjects were excluded due to movement differences. After parameter estimation under restricted maximum likelihood, linear contrasts of parameter estimates were generated for the following first-level contrasts of interest: (i) *No-incentive Anticipation*: anticipation neutral>baseline (ii) *Reward Anticipation*: anticipation win>baseline (ii) *Penalty Anticipation*: anticipation loss>baseline (iv) *Reward Outcome*: feedback win>missed win (v) *Penalty Outcome*: feedback loss>avoided loss. These contrasts were taken forward to whole-brain exploratory group-level random effects analyses described in section 3.8.4.1.

Overall, the aim of the first level analysis is to create an accurate model which best reflects the observed BOLD fMRI time course, thereby minimising the amount of unexplained signal across the voxels in the brain. Indeed, it is important to include all

necessary regressors which are assumed to contribute to the model and exclude regressors that are unrelated to the signal as they can ‘water down’ the model by reducing the degrees of freedom. We used a model which differed to that used in the important study by Admon et al., (2017). Therefore we compared and considered three different approaches and this is detailed in Appendix C. While the models differed we found that significant whole-brain level results remained the same across the three models for the contrasts of interest.

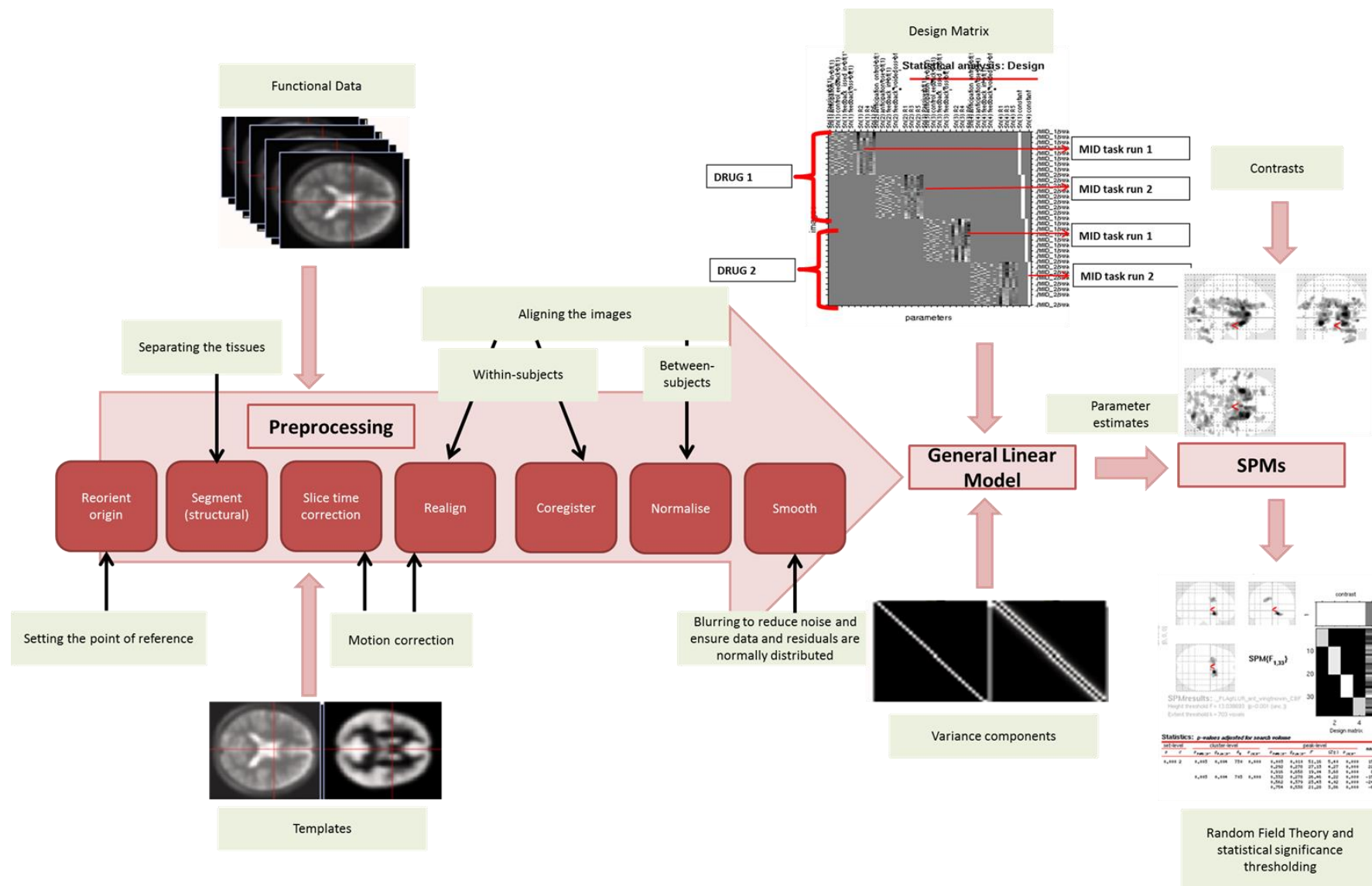


Figure 3.6. An illustrative overview of the pre-processing, first-level and second-level analysis pipeline for the MID task analysis in SPM.

3.8.3.2 ***Modelling Prediction Error***

For the Prediction Error analyses, a second single-subject model was generated. This included four regressors of interest (anticipation phase for all conditions, all gain and all loss outcomes combined, and the neutral condition as 0th order regressors) and motion regressors. For each outcome regressor (wins and penalties), a respective first order parameter was included, modelling win- and penalty-related outcomes in a parametric linear trend by using PE values as parameter inputs (Abler et al., 2006). This analysis is based on a prior MID analysis (Staudinger et al., 2009). Importantly, there were equal numbers of each type of trial within each outcome (i.e. an equal proportion of win outcome to miss win outcome and loss outcome to avoided loss outcome) (See Results Section 4.2). The parametric modulation regressor was mean-corrected by SPM to be orthogonal to the main outcome regressor.

The Prediction Error was calculated as follows:

$$\text{Expected value (EV)} = \text{Magnitude} \times \text{Probability} \quad \text{Equation 2.}$$

$$\text{Prediction Error (PE)} = \text{Outcome} - \text{EV} \quad \text{Equation 3.}$$

Win cues were ascribed a magnitude of +1, whilst penalty cues were ascribed a magnitude of -1. Neutral cues were ascribed a magnitude of 0.

This thesis explores three models that attempt to address different ways in which a participant estimates whether they will receive money or not at any given time point. The first, *Fixed PE model*, used a probability that was set at a fixed value for every trial, (66% for win cues and 34% for penalty cues) in accordance with the tracking algorithm of the MID task. This probability was also chosen on the basis that participants would be (at least) implicitly aware of the success rate when starting the task on the scan day, following their training on the task at the assessment appointment. As shown in Table 3.1, the *Fixed PE model* uses three different PE values.

Table 3.1. Calculation of Prediction Error using a fixed probability of 66% for win cues and 34% for penalty cues on every trial.

Outcome	Prediction Error (PE) calculation: PE = Outcome – EV
Reward/Win Outcome	$1 - (1 \times 0.66) = \mathbf{0.34}$
Missed Win	$0 - (1 \times 0.66) = \mathbf{-0.66}$
Penalty/Loss Outcome	$-1 - (-1 \times 0.34) = \mathbf{-0.66}$
Avoided Loss Outcome	$0 - (-1 \times 0.34) = \mathbf{0.34}$
Neutral Outcome	$0 - (0 \times 0.66) = \mathbf{0}$

However, one could argue that a fixed probability has limited ecological validity as it does not capture the dynamic nature and updating of prediction values in real-time. To address this issue, a second and third *Dynamic PE model* was created using a moving average window. In the second *Dynamic PE model for all cues combined*, the probability was calculated taking into account the success rate of the past *five* trials (win, penalty and neutral trials *combined*). For example, if the hit (hit=1) and miss (miss =0) series for trials *t-5* to *t-1* were [0 0 1 0 1], the expected value (EV) for win trial *t* would be $1 \times (0+0+1+0+1)/5=0.4$ (see Equation 2). At the start of the task, the expected success probability was set at 66% for win cues and 34% for penalty cues, in accordance with the tracking algorithm of the MID task.

In the third model, *Dynamic PE model for reward and penalty cues separately*, the probability was calculated using a dynamic approach and taking into account the success rate of the past *three* trials for win and penalty cues *separately*. For example, if the hit (hit=1) and miss (miss =0) series for win trials *wt-3* to *wt-1* were [0 1 1], the expected value for win trial *wt* would be $1 \times (0+1+1)/3=0.66$. If the hit (hit=1) and miss (miss =0) series for penalty trials *pt-3* to *pt-1* were [0 0 1], the expected value for penalty trial *pt* would be $1 \times (0+0+1)/3=0.33$. As above, at the start of the task, the expected success probability was set at 66% for win cues and 34% for penalty cues. A moving average window of the previous three trials was used because, in a sample of seven trials (which is the average span of working memory), there are likely to be three win trials, in which the participant is tracking the expected value. The justification for separating win and penalty cues is that participants receive instructions separately for win and loss trials. A counter argument for separating win and penalty trials is that participants calculate RPE on a trial-by-trial basis, and the EV

would therefore be formed as an integration of both win and penalty trial information. For this reason, both models were investigated, and all three types of RPE modelling underwent the same group-level analyses described in Section 3.8.4.1.

3.8.4 Statistical modelling: Second (group) Level Analysis

3.8.4.1 *FMRI statistical analysis:*

Anticipation and outcome phases of the MID task

In this section, I begin by describing the brain regions (ROIs) chosen for the main contrasts of interest from the MID task. I then detail the statistical models we used to test hypotheses for reward and penalty anticipation (1a, 1b), outcome (1c, 1d), and, prediction error (2a, 2b). As depression is associated with differential fronto-striatal abnormalities in response to anticipation versus receipt of monetary outcomes (Pizzagalli et al., 2009a), statistical analyses were separately conducted for the cue and outcome phases of the task.

Region of Interest Analyses and Contrasts of interest

To test *a priori* hypotheses (1a, 1b, 1c, 1d, 2a, 2b) regarding fronto-striatal responses to the anticipation and outcome of reward and penalty, a region-of-interest (ROI) analysis was conducted. Mean activations were extracted from seven bilateral anatomical masks of the caudate, putamen, nucleus accumbens (NAcc), orbitofrontal cortex (OFC), anterior cingulate cortex (ACC), insula and amygdala for each participant for the following contrasts of interest: (i) *No-incentive Anticipation*: anticipation neutral>baseline (ii) *Reward Anticipation*: anticipation win>baseline (iii) *Penalty Anticipation*: anticipation loss>baseline (iv) *Reward Outcome*: feedback win>missed win (v) *Penalty Outcome*: feedback loss>avoided loss. This analytic approach has been used previously (Admon et al., 2017) and mitigates possible spillover effects of cue type on the neural responses to outcomes. Masks were collapsed across hemispheres because hemispheric effects on task activation were nonsignificant (all *p* values >.05) and because of the high correlation between hemispheric ROIs. To avoid circular analysis (Kriegeskorte et al., 2009), whole

regions from atlas toolboxes in SPM12 were used (See Figure 3.7) as opposed to defining clusters from the whole brain analysis itself. These ROIs were chosen in accordance with meta-analytical findings of the neural correlates of reward and penalty processing (Bartra et al., 2013; Diekhof et al., 2012; Zhang et al., 2013) and prediction error (Garrison et al., 2013).

It is important to note the implicit assumptions of building ROIs. The use of small, boundary-defined regions, such as the amygdala and NAcc, assumes excellent coregistration and normalisation. For this reason, we applied two different co-registration and normalisation approaches⁷ to the data and used the method with superior alignment (Approach 2), as assessed by visual inspection of 4D files in Mango Multi-image Analysis Software (<http://ric.uthscsa.edu/mango/mango.html>). Moreover, all ROIs were combined with the SPM probabilistic grey matter mask (thresholded at 0.20) to ensure any areas extending into non-grey matter areas such as CSF were removed.

Test of Hypothesis 1: Neural correlates of reward and penalty processing.

Test of Hypothesis 1a: Reward Anticipation. Lurasidone will increase striatal activation during reward anticipation and these effects will be most pronounced in individuals with higher depressive symptoms and anhedonia.

In order to test this hypothesis for normalisation of reward during the anticipation phase of the task by lurasidone, a repeated-measures ANCOVA was performed for each of the seven ROIs. The factors included: *Medication* (placebo, lurasidone) and *Anticipation Cue* (neutral, win, loss) as within-subject variables, *Medication Order* as the between-subject factor, and *Depression Severity* (total BDI score) as the covariate of interest. Evidence in support of hypothesis 1a would be captured by a *Medication-by-Depression Severity-by-Anticipation Cue* interaction, with post-hoc analyses

⁷ **Approach 1** using DARTEL tools (Diffeomorphic Anatomical Registration using Exponentiated Lie Algebra; Ashburner, 2007): Multi-channel segmentation and co-registration to each participant's structural image. A two-step spatial normalization approach was completed in SPM using DARTEL tools. It involved warping the coregistered images to the study-specific template (i.e. the average brain of all participants' data) generated using DARTEL and then normalizing the template onto the Montreal Neurological Institute (MNI-152) template).

Approach 2 using the 'normalize estimate & write' function within SPM12, with the MNI-152 template.

demonstrating this three-way interaction effect specifically for *reward* cues. The threshold for statistical significance is described in Section 3.8.5. In terms of a graphical display, this continuous analysis should show that the difference between striatal neural activity under lurasidone and placebo during reward anticipation is positively correlated with depression severity.

Given that the cardinal symptom of anhedonia in depression best maps onto the anticipatory phase of reward processing (Treadway and Zald, 2011), we also examined whether there were any significant three way interactions with continuous scores of anhedonia, which could otherwise be concealed with the use of total scores in depression severity (which combine together low mood and other symptoms of depression, such as sleep and irritability disturbances). This was assessed by including total scores from the SHAPS and DARS anhedonia questionnaires as covariates of interest.

This ‘omnibus’ analysis, in which all anticipation cues were placed in the same model, allowed us to control for the number of contrasts compared. We expected to find no effect of *Medication Order*.

Test of Hypothesis 1b: Penalty Anticipation. *Lurasidone will alter the penalty-related anticipation signal in ACC, anterior insula, amygdala and striatal regions and these effects will be greatest in individuals with higher depressive symptoms.*

The same ‘omnibus model’ as above was used to test hypothesis 2b. Evidence in support of hypothesis 1b would be captured by a *Medication-by-Depression Severity-by-Anticipation Cue* interaction, with post-hoc analyses demonstrating this three-way interaction effect specifically for *penalty* cues. As this hypothesis is non-directional, the continuous analysis could show that the difference between neural activity under lurasidone and placebo during reward anticipation is either positively or negatively correlated with depression severity.

Test of Hypothesis 1c: Reward Outcome. *Lurasidone will increase the reward feedback signal in the ventral striatum, namely the caudate, putamen and NAcc. These effects will be most pronounced in individuals with higher depressive symptoms.*

Primary continuous analyses: using continuous depression symptoms scores

These primary analyses were conducted with depression measured as a *continuous* variable. To test hypothesis 1c regarding normalisation of reward outcome stage responses, we conducted a repeated measures ANCOVA for each ROI. This included the factors: *Medication* (placebo, lurasidone) and *Outcome Type* (reward, penalty) as within-subject variables, *Medication Order* as the between-subject factor, and *Depression Severity* (total BDI-II score) as the covariate of interest. We predicted that normalisation responses in depressed individuals on lurasidone would be captured by a *Medication-by-Depression Severity-by-Outcome Type* interaction, with post-hoc analyses demonstrating this three-way interaction effect specifically for *reward* outcomes. When visualising the results of this continuous analysis, it should show that the difference between neural activity under lurasidone and placebo during reward anticipation is positively correlated with depression severity.

As is the case for the statistical tests during the anticipation stages of the task, the ‘omnibus’ analysis, in which reward and penalty outcomes are placed in the same model, allows us to control for the number of contrasts compared. We expected to find no effect of *Medication Order*.

As consummatory anhedonia, defined as the lack of pleasure in activities or experiences that used to be pleasant (Treadway and Zald, 2011), best maps onto this reward outcome stage, we also examined whether there were any significant three way interactions with continuous scores of anhedonia. This was assessed by a repeated measures ANCOVA for brain responses to *Reward Outcomes* with factors: *Medication* (placebo, lurasidone) as within-subject variables, *Medication Order* as the between-subject factor, and *Anhedonia Severity* (SHAPS or DARS total score) as the covariate of interest.

Test of Hypothesis 1d: Penalty Outcome. *Lurasidone will reduce the penalty-related feedback signal in the VS, ACC and insula. These effects will be most pronounced in individuals with higher depressive symptoms.*

The same ‘omnibus model’ as above was used to test the hypothesis that lurasidone will reduce the penalty-related outcome signal as a function of depression severity. Evidence in support of hypothesis 2d would be captured by a *Medication-by-Depression Severity-by-Outcome Type* interaction, with post-hoc analyses demonstrating this three-way interaction effect specifically for *penalty* outcome. When visualising the results of this continuous analysis, it should show that the difference between neural activity under lurasidone and placebo during penalty outcome is negatively correlated with depression severity.

Secondary categorical analyses: using BDI-II cut-off scores

As mentioned above, all primary analyses above were conducted using a continuous measure of depression (BDI-II). To complement our dimensional analyses, we also examined our hypothesis regarding normalisation of responses using categorical groups in a repeated measures ANOVA model. We used severity cut-off scores for the BDI-II (Beck et al., 1996; Krefetz et al., 2002; Kumar et al., 2002) to compare individuals with *low depressive symptoms* (Total BDI-II score: 0-16 (normal-mild mood disturbance), n=24) to individuals with *high depressive symptoms* (Total BDI-II score: 17-43 (borderline- severe depression), n=18) on placebo and lurasidone (Ambrosini et al., 1991; Barrera and Garrisonjones, 1988; Canals et al., 2001; Marton et al., 1991; Strober et al., 1981; Whitaker et al., 1990). If our results would be replicated using categorical groups, we would expect a significant *Medication-by-Depression Group-by- Outcome* interaction.

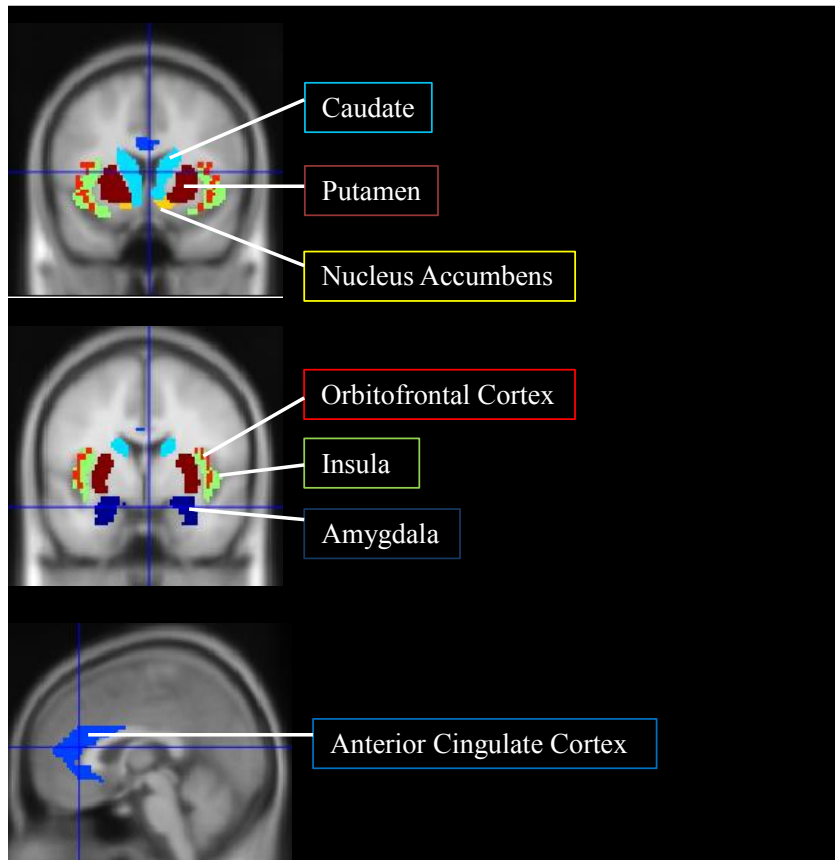


Figure 3.7. Anatomical masks: Location of anatomically defined masks for the Caudate (turquoise), Nucleus Accumbens (NAcc) (yellow), and Putamen (maroon), Orbitofrontal Cortex (OFC) (red), Insula (Green), Amygdala (Indigo), Anterior Cingulate Cortex (ACC) (Blue). The Caudate, putamen, Insula and ACC ROIs were formed from the AAL atlas in SPM. The OFC ROI was formed using Brodmann Area 13 and the NAcc from the IBASPM71 atlas in SPM12.

FMRI Whole-brain analysis for anticipation and outcome phases

The first aim of the whole brain analysis was to test whether the task elicited the expected pattern of activation during reward and penalty anticipation and outcome. (outside the effect of the drug) (Knutson et al., 2001). Thus, whole brain analyses of the entire sample treated as a single group ($n=84$) were conducted for each condition relative to baseline on placebo (i.e., Reward Cue, Penalty Cue, Reward Outcome and Penalty Outcome). This analysis was completed to test whether the task elicited the expected pattern of activation (Knutson et al., 2001). Thresholding and statistical significance levels are described in Section 3.8.5.

The second aim of the whole brain analysis was to model the effects of lurasidone and depression status beyond the fronto-striatal network targeted in the ROI analyses.

Within-subject contrasts were calculated at the first-level for each participant (placebo>lurasidone) and carried forward for a whole brain independent samples t-test at second level with *Medication Order* (placebo-lurasidone, lurasidone-placebo) as the between subject factor and *Depression Severity* as the covariate of interest. The independent samples t-test was conducted separately for the responses to: (i): *No-incentive Anticipation*: anticipation neutral>baseline (ii) *Reward Anticipation*: anticipation win>baseline (iii) *Penalty Anticipation*: anticipation loss>baseline (iv) *Reward Outcome*: feedback win>missed win (v) *Penalty Outcome*: feedback loss>avoided loss.

Thus, the analytical framework for ROI and whole-brain analyses has been described for the anticipation and outcome phases of the task. Next, I will outline the contrasts of interest for the PE analyses which were used to test hypotheses 3b and 3c across the three types of PE models.

Test of Hypothesis 2: Reward and penalty-related Prediction Error.

To test the hypothesis of a restitution of the encoding of PE signaling in individuals with greater depression severity under lurasidone a region-of-interest (ROI) analysis was conducted. Mean activations were extracted from seven bilateral anatomical masks of the caudate, putamen, NAcc, OFC, ACC, insula and amygdala for each participant for the contrasts of interest ‘(win- or penalty-related) prediction error >baseline’. This approach has been utilised previously (Staudinger et al., 2009; Ubl et al., 2015a) and these values were entered into a repeated measures ANCOVA which I describe below. The analyses were completed for all three types of PE model: Fixed PE model, Reward and Penalty PE combined model and the Reward and Penalty cues separate model.

Test of Hypothesis 2a: Reward-related Prediction Error. *Lurasidone will alter (increase or decrease) the reward-related PE signal in the striatum, OFC and ACC. These effects will be most pronounced in individuals with higher depressive symptoms.*

As in the analyses of anticipation and outcome, the analysis of PE utilised an omnibus approach in which both reward and penalty-related PEs were entered into the same model to control for the number of contrasts. To test the non-directional hypothesis 2a, we used a repeated measures ANCOVA, where the within-subject variables included *Medication* (placebo, lurasidone) and *PE Type* (Reward PE, Penalty PE), the between-subject factor included *Medication Order* (placebo-lurasidone, lurasidone-placebo) and *Depression Severity* (total BDI score) score was the covariate of interest. Evidence in favor of an alteration in reward-related PE encoding would be demonstrated by a significant *Medication-by-Depression Severity-by-PE Type* interaction. Specifically, post-hoc analyses should show a *Medication-by-Depression Severity-by-Reward PE* interaction whereby the difference in reward PE encoding under lurasidone and placebo is either positively or negatively correlated with depression severity. We expected no effect of *Medication Order*. Again, statistical significance and thresholding is described in Section 3.8.5.

Test of Hypothesis 2b: Penalty-related Prediction Error. *Lurasidone will alter (increase or decrease) the penalty-related PE signal in frontal, striatal and limbic regions: VS, ACC, amygdala and insula. These effects will be most pronounced in individuals with higher depressive symptoms.*

The same ‘omnibus model’ as above was used to test the hypothesis that lurasidone will reduce the penalty-related PE signal as a function of depression severity. Evidence in support of hypothesis 2b would be captured by a *Medication-by-Depression Severity-by-PE Type* interaction, with post-hoc analyses demonstrating this three-way interaction effect specifically for *penalty-related PE*. When visualised in a graphical format, the continuous analysis should show that the difference in penalty PE encoding under lurasidone and placebo is negatively correlated with depression severity.

FMRI Whole-brain analysis for PE

In addition to the ROI analyses of PE, we conducted a whole-brain analysis to determine which ROIs (caudate, putamen, NAcc, OFC, ACC, insula and amygdala) encode win- and penalty-related PE. This was done for the whole sample across both drugs. These ROIs were chosen as they have previously shown to encode reward- and penalty-related PE (Rothkirch et al., 2017; Ubl et al., 2015b).

3.8.5 Thresholding and statistical Inference

3.8.5.1 ROI analysis statistical threshold

For behavioural and ROI analyses, all statistical tests used were two-tailed with a value of $p < .05$ to denote a significant difference between means. In the case of multiple (seven) ROI comparisons, a Bonferroni correction was made in order to control the Type I error rate (i.e. rejection of a true null hypothesis). Thus, statistical significance was set at $p < .007$ ($0.05/7 = 0.007$) for the ROI analyses.

3.8.5.2 Whole-brain analysis statistical threshold

As detailed in Section 2.1.2.6, the outcome for second level analyses is statistical parametric maps (SPMs) composed of T (or Z) values assigned to every voxel in the brain. Before obtaining these maps it is vital to define an appropriate threshold such that any score which exceeds that threshold has only a small probability of occurring by chance, and can be said to be significantly activated. The large number of independent tests (i.e. one per voxel and a brain scan consists of 10^4 to 10^5 voxels) (Habeck et al., 2008), means that there is a ‘multiple comparison problem’. In standard statistical theory, the Type I error rate is set at $\alpha = 5\%$, so that the likelihood of obtaining a ‘significant’ result and incorrectly rejecting the null hypothesis would occur at a rate of 1 in 20. However, in a statistical map of 120,000 voxels, there will be approximately 6000 voxels activated by chance without correction for multiple comparisons.

A standard way to correct for this family wise error is the Bonferroni correction, whereby the α level is divided by the number of univariate tests completed (see ROI analysis correction above) and this requires that all tests are independent from

each other. However, this is not the case in an fMRI image (due to spatial correlations), and also a Bonferroni correction would lead to a very conservative threshold, thereby increasing the Type II error rate.

Thus, fMRI utilises the principles of Gaussian random field theory (RFT) which allows the selection of a correction threshold whilst simultaneously considering the spatial correlations or smoothness in fMRI data (Asby, 2011). In brief, this approach assumes normality and smoothness in which the greater the smoothness of the image, the less conservative a correction is as the number of resels (resolution elements) decreases. The number of resels is equal to the number of voxels in the image divided by the size (in voxels) of one resel. However, the number of resels does not reflect the number of independent observations in the data. Thus, RFT utilises an equation called the Euler characteristic (EC), which uses the number of resels to give the probability of a suprathreshold intensity peak. The EC assesses the topology of the data and can be defined as the number of activation 'blobs' present after a certain T threshold is set. When the EEC is between 0 and 1, it is equivalent to the probability of having at least one peak above the threshold under the null hypothesis. An EC value of 0.05 is used and a T value that gives an EC value of below 0.05 (which is the corrected FWE α level in SPM) implies that the likelihood that one or more clusters are present at this threshold is below 0.05.

Examining each voxel individually to select out those that exceed this threshold is known as voxel-level inference (i.e. a voxel is significant if its p-value is below the set α level). This is shown in Figure 3.8 and is a very specific level of inference that is useful if one is interested in localised brain activations. In contrast, cluster-level inference defines the significance of a region by taking into account the number of contiguously activated voxels in a particular area. A cluster-forming threshold is set, with contiguous voxels above this threshold then being assessed on a second threshold based on the cluster's size. RFT allows for the calculation of the expected number and size of clusters in a data set, and thus the neuroimaging programme SPM reports both voxel and cluster level statistics. The latter cluster-based thresholding is most often used in the literature due to its superior sensitivity (Friston et al., 1996a).

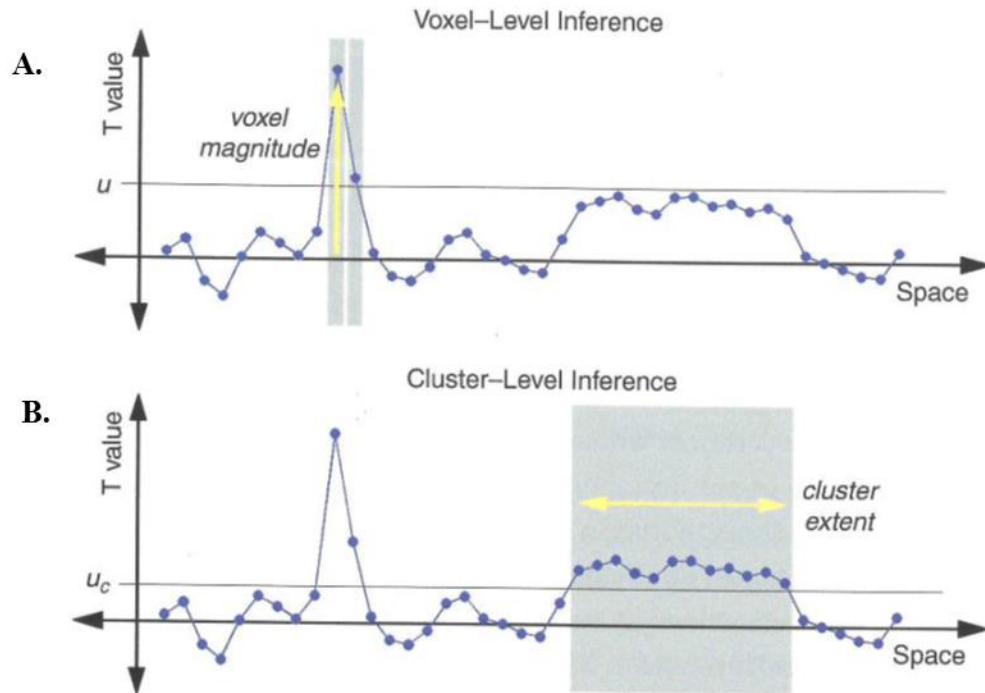


Figure 3.8. Voxel-level (A) versus cluster-level (B) inference. In A, two voxels exceed peak-threshold u . In B, a cluster-forming threshold defines clusters, and one cluster of 12 voxels exceeds height-threshold u_c . None of the voxels are significant alone, but together they comprise a significant cluster. Adapted from Poldrack et al. (2011) with permission.

Importantly, cluster correction relies on the assumption that fMRI data has a constant spatial smoothness over the brain and that the spatial autocorrelation is normally distributed. However, a recent study by Eklund et al., (2016) showed that for a nominal familywise error rate of 5%, parametric statistical methods are shown to be invalid for clusterwise inference as the spatial autocorrelation function does not follow the assumed Gaussian shape. Mainly due to the faulty assumption that the noise spatial autocorrelation function is a Gaussian shape, cluster-based thresholding in SPM produces a false positive rate of up to 25% in an event-related design with 8mm smoothing. By comparison, parametric statistical methods are conservative for voxel-wise inference and can increase the chance of Type-II errors.

The best alternative correction methods are permutation testing (a non-parametric method) and the use of 3DClustSim in Analysis of Functional NeuroImages (AFNI software) (Cox, 1996), since a 'bug' in the software has been fixed (May 2015) (Cox

et al., 2017). 3DClustSim generates a 3D grid of independent and identically distributed $N(0,1)$ random deviates. It smoothes them to the level estimated from the residuals of the fMRI data model at the individual level. It then carries out voxelwise thresholding, and the last step of clustering determines the rate at which contiguous blobs or ‘clumps’ of different sizes occur at the various voxelwise thresholds (.05, .01, .001) (https://afni.nimh.nih.gov/pub/dist/doc/program_help/3dClustSim.html). For example, in our study, whole brain images could be cluster corrected to $p < .050$, (by being required to exceed an extent of 116 continuous voxels), to $p < .010$ (by being required to exceed an extent of 167 continuous voxels), or to $p < .001$ (by being required to exceed an extent of 261 continuous voxels). In line with previous studies, we chose the first option (Gong et al., 2017). Specifically, for the MID task whole brain analyses, results were reviewed with an initial voxel threshold of $p < .001$ and cluster corrected to $p < .05$ by being required to exceed an extent of 116 continuous voxels, as determined by AFNI’s 3DClustSim (Cox et al., 2016; Eklund et al., 2016a). For the ASL whole-brain analyses, statistical significance was set using a conservative threshold of $p < .05$ at the peak voxel-level corrected for multiple comparisons (i.e. Family-wise Error (FWE) corrected) (Friston et al., 1994; Eklund et al., 2016). This is because 3DClustSim cannot be applied to the ASL data using the assumptions of fMRI data.

For all comparisons, brain locations were reported as x, y, and z coordinates in Montreal Neurologic Institute (MNI) space and Wake Forest University (WFU) PickAtlas was used to identify brain regions.

3.8.6 **Test of Hypothesis 3: Sensitivity analyses.**

Test of Hypothesis 3a. Lurasidone’s effects on reward and penalty processing in depression will not be confounded by comorbid anxiety disorders.

In order to test this hypothesis, we first tested for an association between dimensional anxiety scores and brain activation. If there were to be no association, then there would be no need to include it as a covariate in the depression severity ANCOVA models used in hypotheses 1a-2b above (as recommended by Miller and Chapman 2001).

However, if a significant association were to be found, the next step would be to repeat all ROI analyses (repeated measures ANCOVA's for hypotheses 1a-2b) with the following covariates: (i) continuous measures of anxiety (total anxiety score on the HADS); and (ii) current comorbid anxiety disorders (diagnosed using the M.I.N.I and dummy-coded). This analysis approach has been used previously to account for the potential effects of anxiety (Admon et al., 2017; Forbes et al., 2009; Pizzagalli et al., 2009b). Evidence in favour of this hypothesis would mean that adding the anxiety covariates would not influence the pattern or significance of the *Medication-by-Depression Severity-by-Reward/Penalty processing* interaction, thereby indicating that the findings are not driven by current anxiety diagnosis or severity.

Test of Hypothesis 3b. *Lurasidone's effects on reward and penalty processing in depression will not be confounded by self-reported changes in sedation or state-anxiety scores.*

As described in Section 3.2.2, the effects of lurasidone on sedation and state-anxiety were measured at three time points: pre-scan, peak-of-drug and post-scan utilising the VAS and STAI-S questionnaires respectively.

VAS and STAI-S data were analysed using a repeated measures ANCOVA with *Medication* (placebo or lurasidone) as the within-subject variable, *Medication Order* (placebo-lurasidone, lurasidone-placebo) as the between-subject variable, and *Depression Severity* (total BDI score) as the covariate interest. Specifically, we examined the effect of *Medication*, *Medication Order* and *Depression Severity* on the change in *Sedation* ratings (total Visual Analogue Scale (VAS) scores) and *State-anxiety* ratings (total STAI score) from pre-drug administration (Measure 1) to peak-of-drug (Measure 2). Evidence in favour of hypothesis 4c would be shown by non-significant main effects and interactions (i.e. lurasidone would not increase self-reported sedation or state-anxiety scores relative to placebo). We also completed an additional analysis of the VAS in which the 16 scales of the VAS were reduced to two summary factors of Alertness and Tranquillity (Herbert et al., 1976) (see Methods Section 3.2.2). The change in Alertness and Tranquillity ratings from pre-drug to peak-of-drug were then entered into the same repeated measures ANCOVA described above.

Test of Hypothesis 3c. Cerebral Blood flow. *Lurasidone will increase striatal cerebral blood flow in all participants relative to placebo. Lurasidone's effects on reward and penalty processing in depression will not be confounded by baseline shifts in regional and global cerebral blood flow (CBF).*

To test for statistical significant changes in resting CBF, a paired-sample t-test compared the whole-brain CBF maps collected after administration of lurasidone against those acquired after placebo in the whole sample ($n=43$). Next, quantitative measures of global CBF and striatal CBF were extracted for each participant after placebo and lurasidone using the MarsBaR toolbox (<http://marsbar.sourceforge.net>; Brett, Anton, Valabregue, and Poline, 2002). In SPSS, a repeated-measures ANCOVA was performed for global and striatal CBF with the following factors: *Medication* (placebo, lurasidone) as the within-subject variable, *Medication Order* (placebo-lurasidone, lurasidone-placebo) as the between-subject factor, and *Depression Severity* (total BDI score) as the covariate of interest. Evidence in favour of hypothesis 3c would be demonstrated by (i) whole-brain analysis: a statistically significant increase in CBF relative to placebo ($p<.050$ at the peak voxel level corrected for multiple comparisons; see Section 3.8.5 for justification of thresholding and statistical inference) and (ii) ROI analyses: a significant *Medication* - by- *striatal CBF* interaction ($p<.050$).

To test if changes in baseline cerebral blood flow were related to the BOLD findings, the change in global and regional CBF between the lurasidone and placebo visits was entered as covariates in all ROI BOLD fMRI analyses. Evidence in favour of hypothesis 3c would be shown by the fMRI BOLD results remaining unchanged when controlling for the predicted increases in regional and global cerebral blood flow (CBF) under lurasidone at baseline.

Chapter 4 - Results

In the Results chapter of this thesis, I begin by summarising the participant characteristics and the behavioural results of the study which include performance data of the Monetary Incentive Delay Task. These analyses are important to set the framework for understanding the neuroimaging findings. I then examine the results for the three hypotheses tested in this thesis for the effect of lurasidone on (1) neural correlates of reward and penalty processing and (2) reward and penalty-related prediction error signal and (3) cerebral blood flow (CBF) in depression (see Table 1.12 in Introduction Section 1.8.2 and Figure 4.1 below). I then evaluate the robustness of these findings by completing a host of sensitivity analyses to ensure that lurasidone's effects on reward and penalty processing in depression are not be confounded by anxiety, self-reported changes in sedation or state-anxiety scores from pre-drug administration (Measure 1) to peak-of-drug (Measure 2) and baseline shifts in regional and global CBF. A map of the results section can be found in Figure 4.1 below.

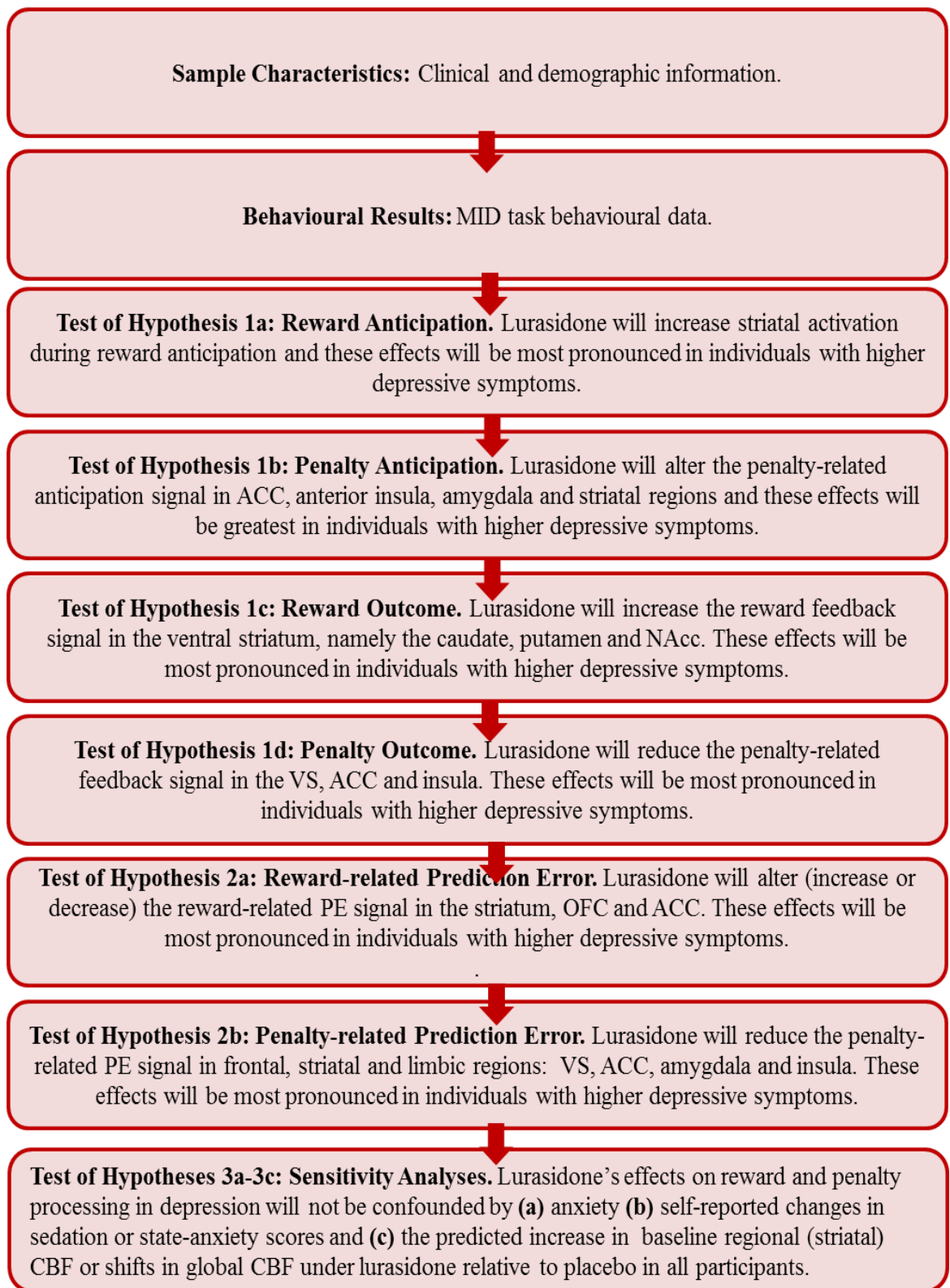


Figure 4.1. Map of Results Chapter

4.1 Participant characteristics

4.1.1 Depressive symptoms and characteristics

Before examining the behavioural and neuroimaging results, it is useful to have an overview of the participant characteristics in the study sample.

As detailed in Methods Section 3.8.4.1, all analyses were completed using continuous measures in depression severity. Table 4.1 provides demographic and clinical information for the entire sample ($n=43$). However, for the purpose of visualising complex interactions in the analyses below (e.g. Medication-by-Depression Severity-Behaviour/Brain data), we also used depression severity cut-off scores from the Beck's Depression Inventory-II (Beck et al., 1996; Krefetz et al., 2002; Kumar et al., 2002): individuals with *low depressive symptoms* (Total BDI-II score: 0-16 (normal-mild mood disturbance), $n=24$) versus *high depressive symptoms* (Total BDI-II score: 17-43 (borderline-severe depression), $n=18$) (Ambrosini et al., 1991; Barrera and Garrisonjones, 1988; Canals et al., 2001; Marton et al., 1991; Strober et al., 1981; Whitaker et al., 1990). Thus, Table 4.2 provides demographic and clinical characteristics of recruited participants according to these depression severity cut-off scores. When the sample is split into low and high depression severity groups, they differ significantly in depression scores (BDI-II ($t(39)=8.58$, $p<.001$) and HADS Depression Score ($t(41)=10.64$, $p<.001$)), in anhedonia scores (SHAPS ($t(39)=6.69$, $p<.001$) and DARS ($t(41)=10.64$, $p<.001$) scales) and in anxiety symptoms (HADS Anxiety Score ($t(41)=8.00$, $p<.001$)).

Given that all participants completed the Mini International Neuropsychiatric Interview version 6.0.0 (M.I.N.I) (Sheehan et al., 1998), we also examined the convergence between continuous BDI-II scores and depression diagnoses as assessed by psychiatric interview (Please refer to Methods Section 3.1 for details of diagnostic criteria for subthreshold and MDD). As shown in Table 4.2 and Figure 4.2, the same individuals who scored highly on the BDI-II also could be diagnosed as having subthreshold or full-criteria MDD. This suggests that the BDI-II scale is a good indicator of depression severity.

Figure 4.3 shows the spread of anhedonia scores in the sample. Individuals with higher depression severity had higher self-reported anhedonia, however, when assessing subthreshold and MDD diagnoses across continuous anhedonia scores, some individuals with subthreshold depression had higher anhedonia scores than some individuals with MDD. This is not unusual as MDD is a heterogeneous disorder and patients may primarily show difficulties with low mood as opposed to anhedonia.

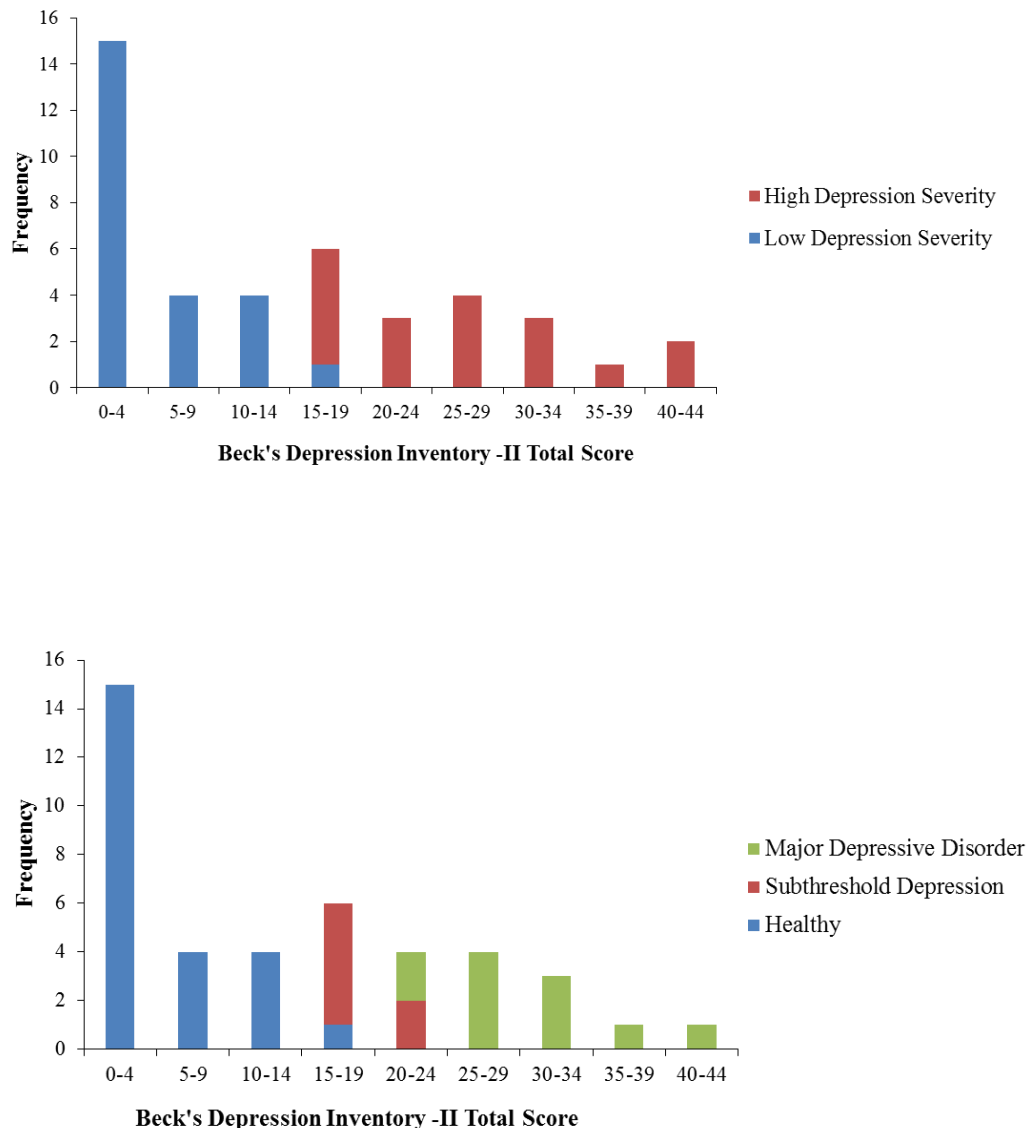
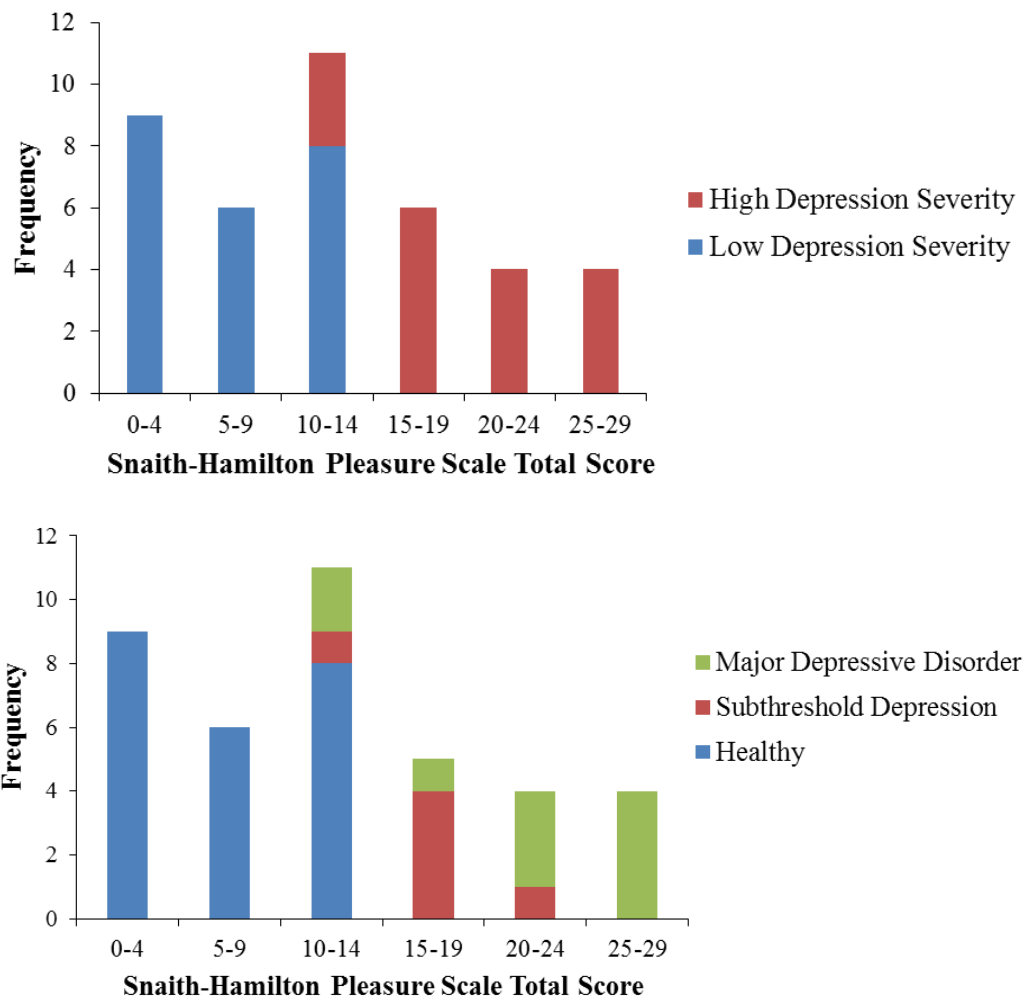


Figure 4.2. Histogram showing the frequency of Beck's Depression Inventory (BDI-II) Total Scores in the sample organized by (A) Depression severity cut-off scores from the Beck's Depression Inventory-II: individuals with low depressive symptoms (Total BDI-II score: 0-16 (normal-mild mood disturbance), $n=24$) versus *high depressive symptoms* (Total BDI-II score: 17-43 (borderline-severe depression), $n=18$); (B) Diagnosis as assessed by the Mini International Neuropsychiatric Interview version 6.0.0 (M.I.N.I): (*Healthy*: $n=24$, *Subthreshold Depression*: $n=7$, *Major Depressive Disorder*: $n=11$). The positive skew in the distribution of BDI-II scores in

our sample is consistent with studies completed in the general population (n=1250) (Lasa et al., 2000).



*Figure 4.3. Histogram showing the frequency of Anhedonia Scores in the sample as measured by the Snaith-Hamilton Pleasure Scale (SHAPS) organized by (A) Depression severity cut-off scores from the Beck's Depression Inventory-II: individuals with *low depressive symptoms* (Total BDI-II score: 0-16 (normal-mild mood disturbance), n=24) versus *high depressive symptoms* (Total BDI-II score: 17-43 (borderline-severe depression), n=18); (B) Diagnosis as assessed by the Mini International Neuropsychiatric Interview version 6.0.0 (M.I.N.I): (*Healthy*: n=24, *Subthreshold Depression*: n=7, *Major Depressive Disorder*: n=11).*

Table 4.1. Demographic and clinical characteristics of participants in a study investigating the effect of lurasidone on reward and penalty processing.

Characteristic	Participants (N=43)	
	Mean	SD (range)
Age (years)	21.83	2.05 (18-25)
Beck Depression Inventory – II	13.89	12.83 (0-43)
Snaith-Hamilton Pleasure Scale	12.18	8.49 (0-29)
Dimensional Anhedonia Rating Scale	28.99	22.74 (0-77)
Hospital Anxiety and Depression Scale (Depression score)	4.68	4.85(0-15)
Hospital Anxiety and Depression Scale (Anxiety score)	7.00	5.86(0-21)
	N	%
Female	28	65.12
Caucasian	36	83.72
Current subthreshold depression	7	16.28
Current MDD	11	25.58
Lifetime MDD	15	34.88
Lifetime MDD and Current subthreshold depression	5	16.28
Lifetime MDD and Current MDD	10	23.26
Current comorbid anxiety disorders	10	23.26

Table 4.2. Demographic and clinical characteristics of recruited participants according to depression severity cut-off scores from the Beck's Depression Inventory-II: individuals with low depressive symptoms (Total BDI-II score: 0-16 (normal-mild mood disturbance), n=24) versus *high depressive symptoms* (Total BDI-II score: 17-43 (borderline-severe depression), n=18). This table shows the convergence between BDI-II scores and depression diagnoses as assessed by the Mini International Neuropsychiatric Interview version 6.0.0 (M.I.N.I) (Sheehan et al., 1998).

Characteristic	High Depression Symptoms ^a (N=18)		Low Depression Symptoms ^b (N=24)		Test	p-value
	Mean	SD	Mean	SD		
Age (years)	21.33	2.43	22.32	1.65	T-test (dof)	.096
Beck Depression Inventory – II	26.44	8.79	4.86	5.01	-8.58(39)	<.001
Snaith-Hamilton Pleasure Scale	19.12	6.01	7.21	5.99	-6.69(39)	<.001
Dimensional Anhedonia Rating Scale	48.55	18.65	13.86	12.19	-7.13(39)	<.001
Hospital Anxiety and Depression Scale (Depression score)	8.80	3.47	0.78	0.95	-10.64(41)	<.001
Hospital Anxiety and Depression Scale (Anxiety score)	11.75	4.82	2.91	2.07	-8.00(41)	<.001
	N	%	N	%	χ^2	
Female	13	72.22	15	62.50	.000	.988
Caucasian	15	83.33	20	83.33	.380	.538
Current subthreshold depression	7	38.88	0	0.00		
Current MDD	11	61.11	0	0.00		
Lifetime MDD	15	83.33	2	8.33		
Lifetime MDD and Current subthreshold depression	5	27.77	0	0.00		
Lifetime MDD and Current MDD	10	55.55	0	0.00		
Current comorbid anxiety disorders	10	55.55	0	0.00		

Individuals with ^a *High Depression Severity* (Total BDI-II score: 17-43 (borderline- severe depression), n=18) and ^b *Low Depression Severity* (Total BDI-II score: 0-16 (normal-mild mood disturbance), n=24) according to depression severity cut-off scores for the BDI-II (Beck et al., 1996; Krefetz et al., 2002; Kumar et al., 2002).

All participants were right-handed, per inclusion criteria. MDD: Major Depressive Disorder. Subthreshold and current and lifetime MDD and Anxiety Disorders diagnosed by the Mini International Neuropsychiatric Interview version 6.0.0 (M.I.N.I) (Sheehan et al., 1998).

4.2 Behavioural results from the Monetary Incentive Delay task

Performance in the Monetary Incentive Delay (MID) task was assessed according to five parameters: (i) *No Responses* (ii) *Premature Responses* (iii) *Total Winnings*, (iv) *Mean Reaction Time (RT)* and (v) *Accuracy* for the three cue types: reward, penalty and neutral (no-incentive). A repeated measures ANCOVA with *Medication* (placebo or lurasidone) and *Cue Type* (Reward, Penalty, Neutral) as the within-subject variables, *Medication Order* (placebo-lurasidone, lurasidone-placebo) as the between-subject variable, and *Depression Severity* (total BDI score) as the covariate interest was completed for (i) *No Responses* (ii) *Premature Responses* (iii) *Total Winnings*, (iv) *Mean Reaction Time (RT)* and (v) *Accuracy*. Performance data are presented in Table 4.3.

4.2.1 Adherence to task

4.2.1.1 Response Rate

We first examined response rate, (defined as a button press within the entire 700 ms response window), across each trial type (reward, penalty and neutral cues) and for each treatment session to ensure that data was only included from participants who were actively and appropriately engaged in the task. We found that one participant (with low depression severity) failed to make a button response to neutral cues on one run of the MID task at the placebo visit. This reduction in response rate can be seen for participant 6 in Figure 4.4. Thus, this participant was excluded from behavioural and subsequent neuroimaging analyses, as their inclusion would invalidate RT and accuracy data as a result of their non-adherence to the task. The remaining participants had high response rates, with the maximum number of no responses on any full run of the MID task being 7 of 104 trials (thus giving a 93.3% response rate) (Figure 4.4). This suggests that across all sessions, participants maintained engagement throughout the duration of the task.

We also examined response rate between reward, penalty and neutral cues. We found a significant *Cue Type-by-Number of No Responses* interaction ($F(2,78)=13.19$, $p>.001$), with no interactions with *Medication* or three-way interactions (all p values >

.050). Post-hoc tests showed that the effect of cue type was due to a higher number of no responses to neutral cues relative to either reward cues ($p = .001$) or penalty cues ($p = .001$). A similar result was found in the accuracy analyses (Section 4.2.4 below).

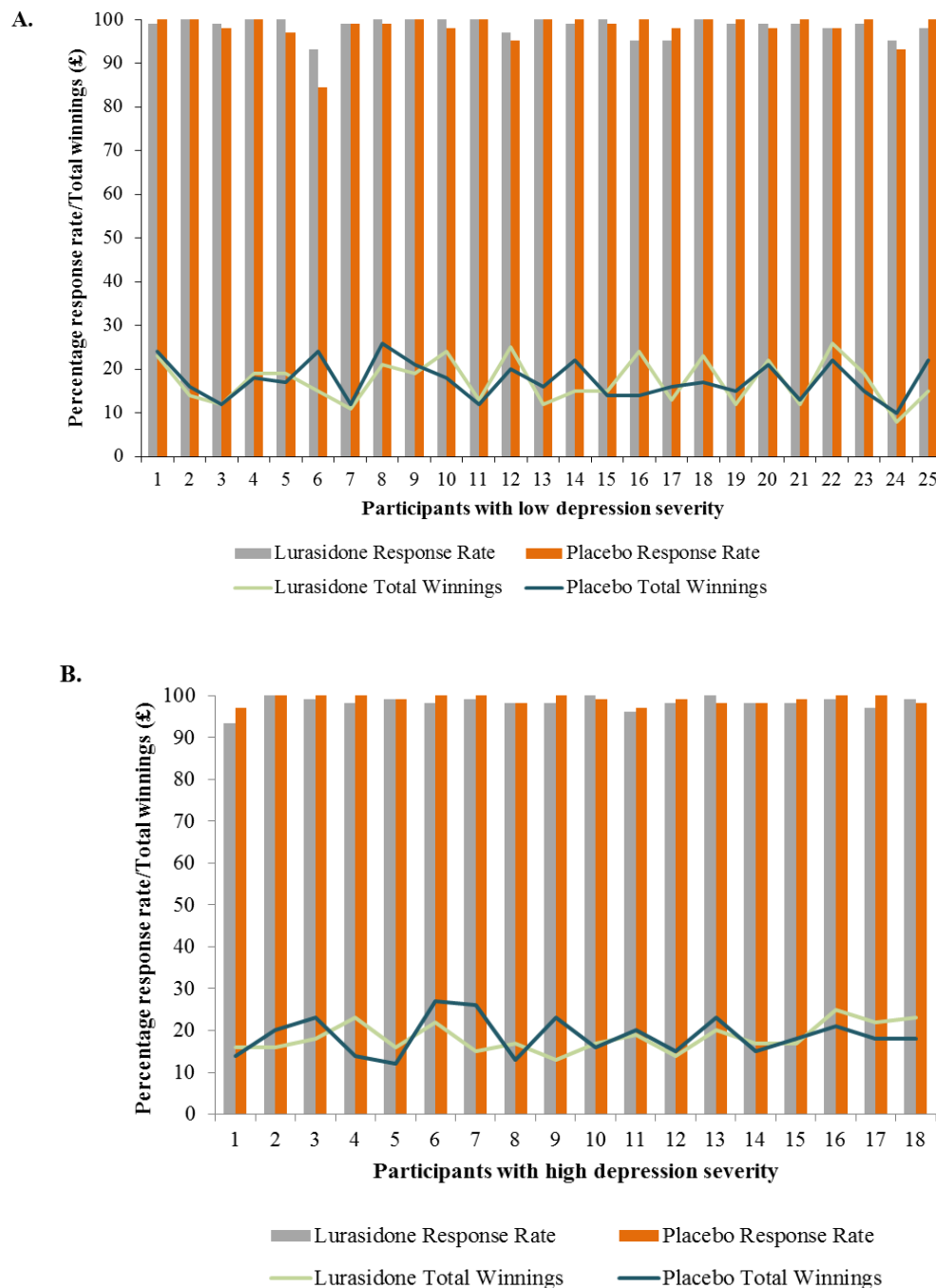


Figure 4.4. Response rate and total winnings across placebo and lurasidone visits according to depression severity cut-off scores from the Beck's Depression Inventory-II: individuals with (A) *low depressive symptoms* (Total BDI-II score: 0-16 (normal-mild mood disturbance), $n=25$) versus (B) *high depressive symptoms* (Total BDI-II score: 17-43 (borderline-severe depression), $n=18$).

4.2.1.2 *Premature responses*

We also examined the number of trials in which the RTs were less than 100 ms (i.e. premature responses). Responses greater than 700 ms (i.e. late responses) were not recorded as this exceeded the maximum response target window (see Figure 3.5 of the MID task in Methods Section 3.5). There was a low overall rate of premature responses for both drug sessions (mean number of trials with premature responses: placebo: 1.52%, SD: 2.39; lurasidone: mean: 1.05%, SD: 1.84). However, we found a significant *Cue Type-by-Number of Premature Responses* interaction ($F(2,80)=4.78$, $p=.011$). Post-hoc tests showed that the effect of cue type was due to a higher number of premature responses to penalty cues relative to neutral cues ($F(1,40)=9.76$, $p=.003$), but not relative to reward cues ($F(1,40)=3.61$, $p=.065$). This perhaps suggests greater readiness to respond rapidly when there is the prospect of losing money relative to a no-incentive cue.

Interestingly, we also found a *Medication-by-Cue Type -by-Number of Premature Responses* interaction ($F(2,80)=4.04$, $p=.021$). This indicates that medication had different effects on the number of premature responses depending on the cue type. To break down this interaction, contrasts were performed comparing reward and penalty cues to neutral cues (the baseline) and reward to penalty cues for lurasidone compared to placebo. These revealed significant interactions when comparing penalty cues to neutral cues for lurasidone compared to placebo ($F(1,40)=4.54$, $p=.039$), and reward cues to penalty cues ($F(1,40)=7.24$, $p=.010$) but not when comparing reward cues to neutral cues ($F(1,40)=0.01$, $p=.913$). As shown in the interaction graph in Figure 4.5, this reflects that premature responses are lower on lurasidone compared to placebo and that the increase in premature responses compared to neutral trials is reduced by lurasidone. This was not the case for reward versus neutral trials. This fits with lurasidone making participants less loss averse, even though the number of premature responses was quite low. There were no significant interactions with depression severity or medication order (all $p > .050$). Overall, this suggests that lurasidone reduced the number of premature anticipatory responses to a target, following the display of a penalty cue, regardless of depressive symptom severity. Although lurasidone had this effect on premature responses, it did not alter mean RTs, as

described in Section 4.2.3. The premature responses (<100 ms) were subsequently excluded from the mean RT calculation, but still included in the accuracy calculations.

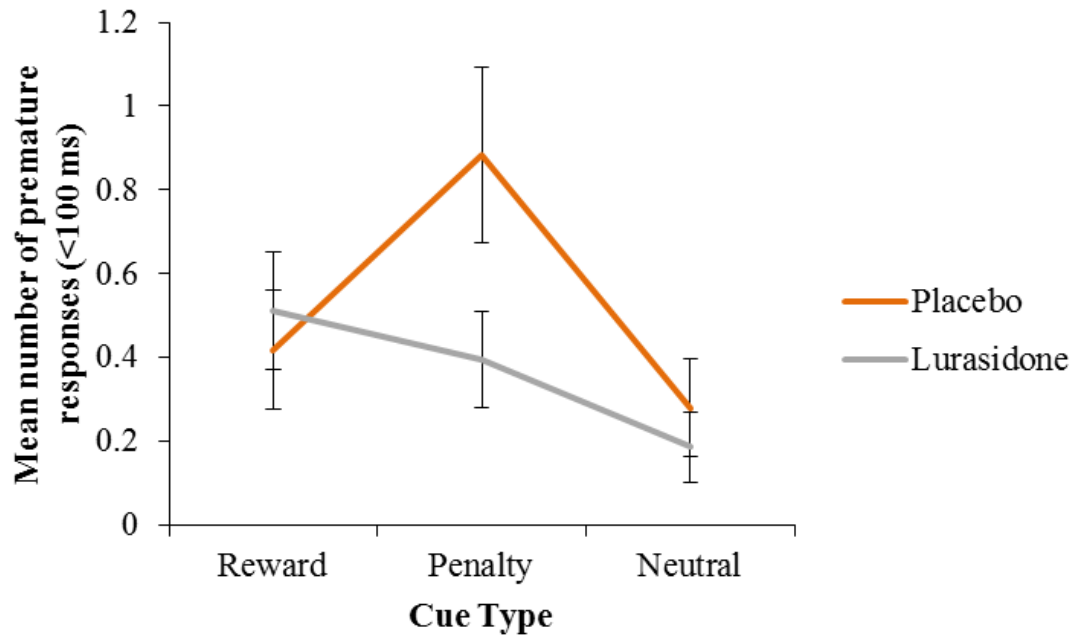


Figure 4.5. Graph illustrating the Cue Type-by- Medication-by-Number of Premature Responses interaction.

4.2.2 Total Winnings

As shown in Table 4.3 and Figure 4.4, the total winnings, across the two runs of the MID task were similar between lurasidone and placebo across the whole sample (*Total Winnings and Medication* ($F(1,40)=0.03, p=.847$)), with a mean of £18 being won under both medications. The ANCOVA also revealed no significant interactions between *Total Winnings* and *Depression Severity* ($F(1,40)=0.72, p=.403$) or *Total Winnings-by-Depression Severity-by-Medication* ($F(1,40)=0.04, p=.480$).

Table 4.3. Performance data of the Monetary Incentive Delay (MID) task, split by Medication.

	Medication, Mean (SD)		Repeated Measures ANCOVA (Medication-by-Depression Severity)	
	Placebo ^a	Lurasidone ^b	F value	P value
Total Winnings, (£)	17.98(4.42)	17.70(4.51)	0.05	.463
Success, %				
Overall	59.24(6.09)	59.15(5.86)	0.11	.740
Neutral trials	47.05(8.91)	47.85(9.01)	0.58	.452
Win Trials	68.25(9.27)	67.71(9.94)	0.45	.506
Loss trials	62.43(10.08)	61.90(11.07)	0.24	.624
Reaction time, ms				
Neutral Outcome	269.70(26.78)	275.70(27.79)	0.17	.681
Missed Neutral Outcome	319.40(50.43)	335.70(59.13)	0.20	.659
Reward/Win Outcome	253.00(21.75)	259.80(25.38)	0.31	.580
Missed Win Outcome	273.10(52.23)	292.60(51.67)	3.98	.054
Penalty/Loss Outcome	269.80(46.12)	293.60(55.59)	0.00	.960
Avoided Loss Outcome	249.60(23.19)	253.90(23.22)	0.05	.824
Change^c in Sedation	-26.19(141.42)	-85.07(151.40)	1.18	.284
Change^c in State-Anxiety	0.52(4.88)	-0.95(3.78)	3.64	.064

^a Individuals with Low Depression Severity (BDI scores <16) and High Depression Severity (BDI scores ≥17) on Placebo.

^b Individuals with Low Depression Severity (BDI scores <16) and High Depression Severity (BDI scores ≥17) on Lurasidone.

^c Change score from pre-drug administration (Measure 1) to peak-of-drug (Measure 2), approximately three hours after drug administration.

A repeated measures ANCOVA with *Medication* (placebo or lurasidone) as the within-subject variable, *Medication Order* (placebo-lurasidone, lurasidone-placebo) as the between subject variable and *Depression Severity* (total BDI score) as the covariate interest was completed for (i) *Total Winnings*, (ii) *Accuracy* and (iii) *Mean Reaction Time (RT)* to the target on win, neutral and loss trials.

4.2.3 Mean reaction Time

Analysis of mean RT revealed a *Cue Type-by-Mean RT* interaction ($F(2,74)=55.39$, $p>.001$), with no interactions with *Medication* or three-way interactions (all p values > .050). The effect of cue type was driven by longer reaction time to neutral cues relative to either reward cues ($p < .001$) or penalty cues ($p < .001$). This reflects motivated responding on reward and penalty trials versus neutral trials across the

entire sample. The same pattern remained when separating the sample into groups using medication type and BDI median split (Low Depression Severity: BDI scores 0-16; High Depression severity: BDI scores >17).

4.2.4 Accuracy

Analysis of accuracy showed a significant *Cue Type*-by-*Accuracy* interaction ($F(2,80)=55.39, p>.001$), with no interactions with *Medication* or three-way interactions (all p values > .050). Post-hoc tests showed that the effect of cue type was due to lower accuracy to neutral cues relative to either reward cues ($p < .001$) or penalty cues ($p < .001$). The groups also did not differ in the percentage of reward trials ending in gains or the percentage of loss trials ending in penalties (i.e. *Outcome Frequency*). This result is of particular importance for the RPE analyses described in Section 4.3.8 because it suggests that the probabilities calculated for the tracker were accurate. Specifically, a mixed-effects ANOVA with *Outcome Type* (Win, No-Win, Loss, No-Loss, No Change) and *Medication* (placebo, lurasidone) as within-subject variables, *Medication Order* as a between-subject variable, and *Depression Severity* as the covariate of interest, revealed only a main effect of *Outcome Type* ($F(2,80)=39.06, p < .001$). Post-hoc contrasts showed that this main effect was due to a higher frequency of Win relative to Missed Win outcomes following a reward cue ($p < .001$), and a higher frequency for Avoided Loss relative to Loss following the penalty cue ($p < .001$). These results are consistent with the task tracker which intends to ensure approximately 66% successful trials – Win or Avoided Loss – for all participants. The analyses of the reaction time and accuracy (outcome frequency), suggest that the BOLD fMRI findings were not confounded by group differences in task difficulty.

4.2.5 Summary of behavioural results

Overall, analysis of behavioural performance on the MID task showed that there was good task adherence (high reponse rate and low number of premature responses) across the entire sample, albeit one participant. We found that relative to placebo, lurasidone reduced the number of premature responses to penalty cues relative to neutral cues. However, there were no significant effects of medication on reward and

penalty processing performance (total winnings, RTs and Accuracy). Instead, we found an effect of cue type on RT and accuracy such that there were faster and more accurate responses to reward and penalty cues relative to no-incentive cues.

4.3 **BOLD fMRI results of the MID task**

To test *a priori* hypotheses (1a, 1b, 1c, 1d, 2a, 2b) regarding fronto-striatal responses to the anticipation and outcome of reward and penalty, we utilised a region-of-interest (ROI) analysis. These regions included the caudate, putamen, nucleus accumbens (NAcc), orbitofrontal cortex (OFC), anterior cingulate cortex (ACC), insula and amygdala. For all the analyses below we predicted that task-related activations to rewards and penalties would be modulated by medication and depressive symptoms. I begin by exploring the results of the anticipatory phase before describing the neuroimaging results for the outcome phase of the task. Before embarking on drug and depression effects, it is important to mention that analysis of the main effects of the task showed activations as expected and these whole-brain results are detailed in Section 4.3.7.

4.3.1 **Anticipation Phase**

A repeated-measures ANCOVA was performed for each of the seven ROIs. The factors included: *Medication* (placebo, lurasidone) and *Anticipation Cue* (neutral, win, loss) as within-subject variables, *Medication Order* as the between-subject factor, and *Depression Severity* (total BDI score) as the covariate of interest. We controlled for the number of experimental contrasts by including all cue types in the model (i.e. an ‘omnibus’ model).

4.3.2 **Test of Hypothesis 1a: Reward Anticipation.** *Lurasidone will increase striatal activation during reward anticipation and these effects will be most pronounced in individuals with higher depressive symptoms and anhedonia.*

In contrast to the hypothesis, there were no significant *Medication-by-Depression* interactions in the anticipation phase of the task. Instead, the repeated measures ANCOVA revealed a significant *Medication-by-Anticipation Cue* interaction in the

ACC ($F(2,72)=8.16, p=.001$) and caudate ($F(2,72)=7.78, p=.001$). Contrary to expectations, post-hoc tests show that lurasidone reduced neural activity to win cues versus placebo, and increased responses for neutral cues in the ACC ($F(1,37)=7.03, p=.012$) and caudate ($F(1,37)=7.58, p=.009$) (see Figure 4.6). The *Medication-by-Anticipation Cue* interaction fell short of significance in the NAcc ($F(2,72)=4.90, p=.010$), OFC ($F(2,72)=3.94, p=.024$) and amygdala ($F(2,72)=3.85, p=.026$) after Bonferroni corrections for multiple ROI comparisons (statistical significance set at $p<.007$).

Given that the cardinal symptom of anhedonia in depression best maps onto the anticipatory phase of reward processing (Treadway and Zald, 2011), we also examined whether there were any significant three way interactions with continuous scores of anhedonia, which could otherwise be concealed with the use total depression severity scores which combine various symptoms of depression. This was assessed by including total scores from the SHAPS and DARS anhedonia questionnaires as covariates of interest.

In this analysis, we also did not find a modulation of reward-related anticipatory responses by lurasidone in individuals with more severe scores. The same *Medication-by-Anticipation Cue* results as above were found, with lurasidone reducing neural activity to win cues versus placebo, and increasing responses for neutral cues in the ACC ($F(1,37)=6.90, p=.013$) and caudate ($F(1,37)=10.71, p=.002$).

4.3.3 **Test of Hypothesis 1b: Penalty Anticipation.** *Lurasidone will alter the penalty-related anticipation signal in ACC, anterior insula, amygdala and striatal regions and these effects will be greatest in individuals with higher depressive symptoms.*

As described above, the omnibus model did not reveal that lurasidone's strongest effects occurred in individuals with higher depressive symptoms. The analyses did however show that lurasidone reduced neural activity to penalty cues versus placebo, and increased responses for neutral cues in the ACC ($F(1,37)=6.86, p=.013$) and caudate ($F(1,37)=5.32, p=.027$) across the entire sample (i.e. regardless of depressive symptoms) (Figure 4.6).

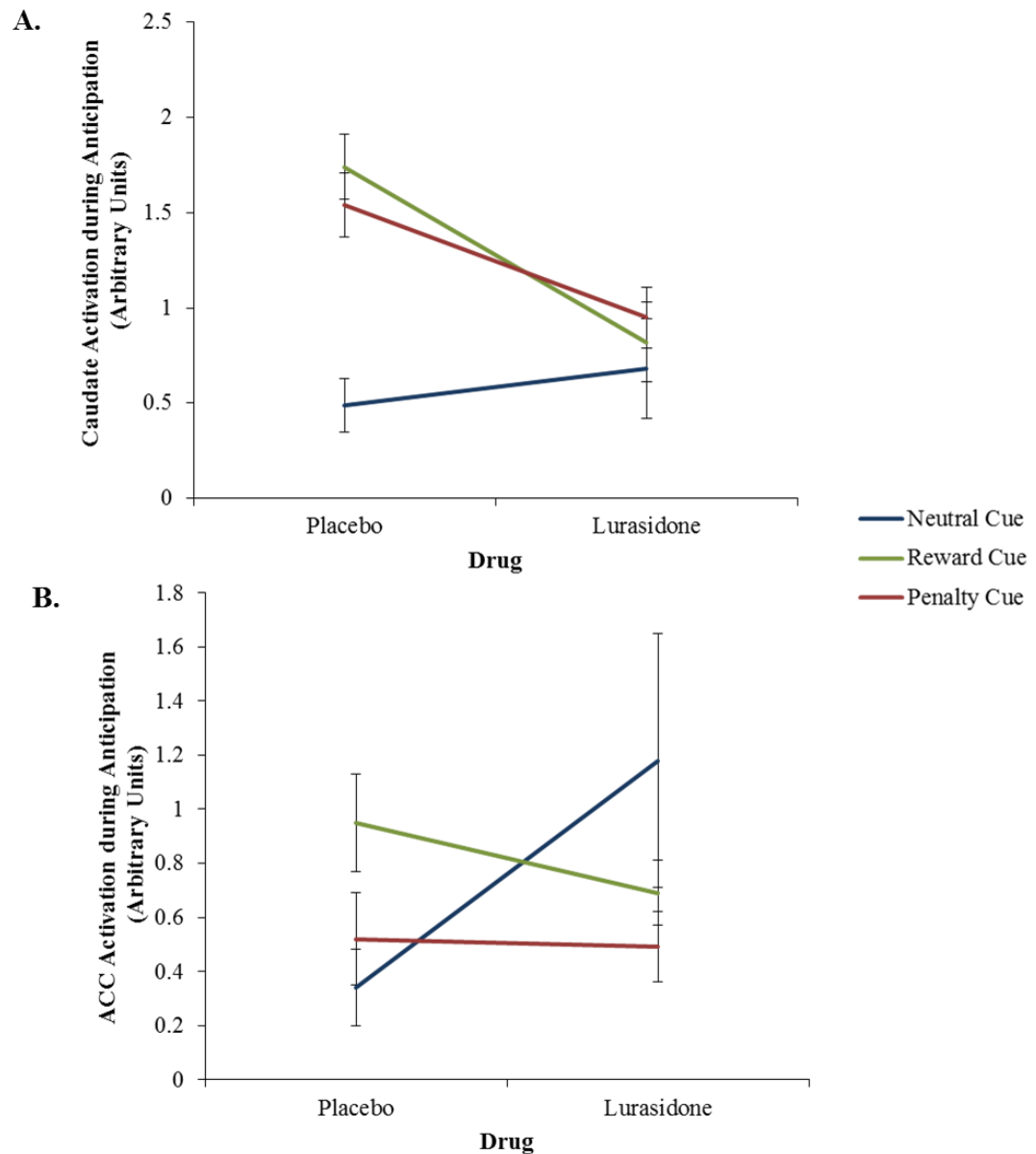


Figure 4.6. Medication-by-Anticipation Cue interaction in (A) caudate ($F(2,72)=7.78$, $p=.001$) and (B) ACC ($F(2,72)=8.16$, $p=.001$). Lurasidone reduced neural activity to Reward and Penalty cues versus placebo, and increased responses for neutral cues in the caudate and ACC.

4.3.4 Outcome Phase

The outcome phase of the task involved participants receiving feedback about their performance on that particular trial and their cumulative total winnings.

4.3.4.1 ***Primary continuous analyses: using continuous depression symptoms scores***

These primary analyses were conducted with depression measured as a *continuous* variable. In order to test (hypothesis 1c) that lurasidone would increase activation to reward outcomes and (hypothesis 1d) decrease responses to penalties in depressed individuals, we conducted a repeated-measures ANCOVA. We controlled for the number of experimental contrasts by including both types of outcome (reward and penalty) in the model (i.e. an ‘omnibus’ model). Specifically, *Medication* (placebo, lurasidone) and *Outcome Type* (*Reward Outcome* versus *Penalty Outcome*) were the within-subject variables, *Medication Order* was the between-subject factor, and *Depression Severity* (total BDI-II score) was the covariate of interest (n=40). Two participants were excluded from this analysis for the following reasons (i) one (high depression severity) participant had ACC and NAcc mean activation values that were greater than three standard deviations from the group mean for the *Reward Outcome* contrast and (ii) one (low depression severity) participant had ACC mean activation values that were greater than three standard deviations from the group mean for the *Penalty Outcome* contrast. (However, see Section 4.3.5 for analyses in which these participants are included).

Unlike the anticipation phase of the task, in the outcome phase, the repeated measures ANCOVA revealed a significant *Medication-by-Depression Severity-by-Outcome Type* interaction in the anterior cingulate cortex (ACC) ($F(1,37)=8.10, p=.007$), after passing Bonferroni adjustment for seven multiple ROI comparisons. The interaction fell short of Bonferroni-adjusted significance in the NAcc ($F(1,37)=3.98, p=.044$), orbitofrontal cortex (OFC) ($F(1,37)=4.47, p=.041$) and Insula ($F(1,37)=4.90, p=.033$). There were no significant interactions with *Medication Order* (all p values > .050).

To understand the significant three-way interaction, we conducted two repeated-measures ANCOVAs for *Reward Outcome* (n=41) and *Penalty Outcome* separately (n=41 after excluding outliers).

4.3.4.2 **Test of Hypothesis 1c: Reward Outcome.** *Lurasidone will increase the reward feedback signal in the ventral striatum, namely the caudate, putamen and NAcc. These effects will be most pronounced in individuals with higher depressive symptoms and consummatory anhedonia.*

When we examined the *Medication-by-Depression Severity-by-Reward Outcome* interaction across the seven ROIs we found that lurasidone had its strongest effect of *increasing* responses to reward outcomes in individuals with high depression severity. Figure 4.7 and Figure 4.8 demonstrate that under placebo, individuals with higher depressive symptoms had attenuated ACC and NAcc activity during positive feedback. In contrast, under lurasidone, the same individuals had increased reward-related ACC and NAcc activity. Despite the clarity of this trend in the interaction graph below, the trend fell short of Bonferroni-adjusted significance in the Nucleus Accumbens ($F(1,38)=4.87, p=.033$) and ACC ($F(1,37)=5.92, p=.020$).

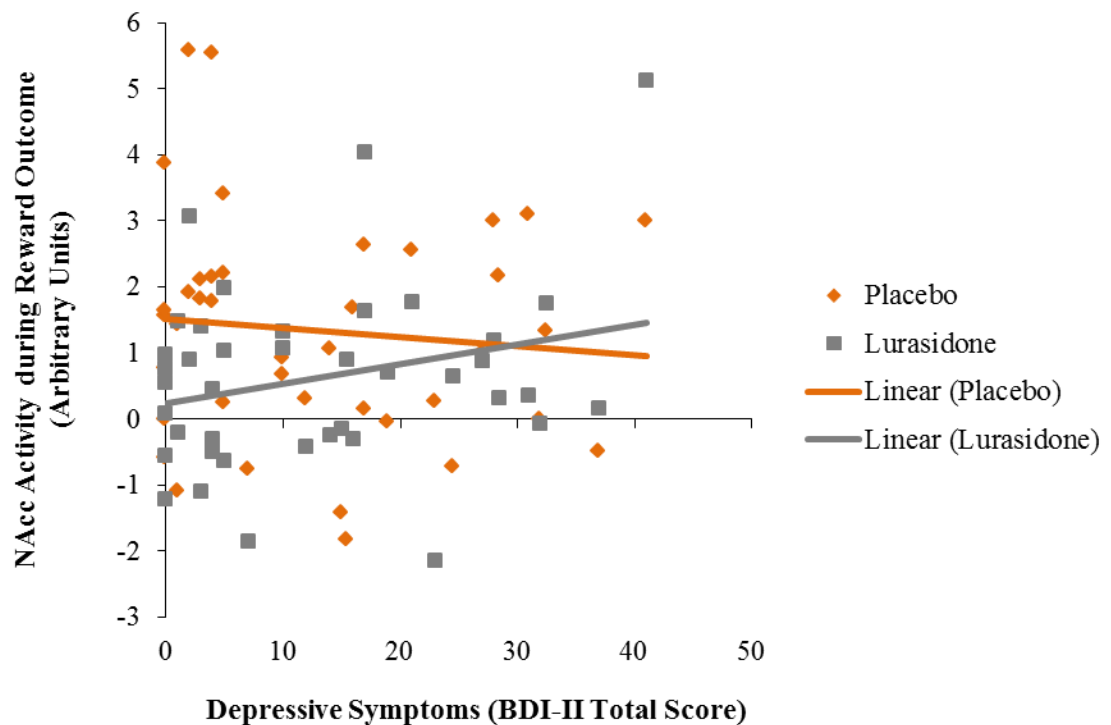


Figure 4.7. NACC response during Reward Outcome across continuous depression scores under lurasidone and placebo.

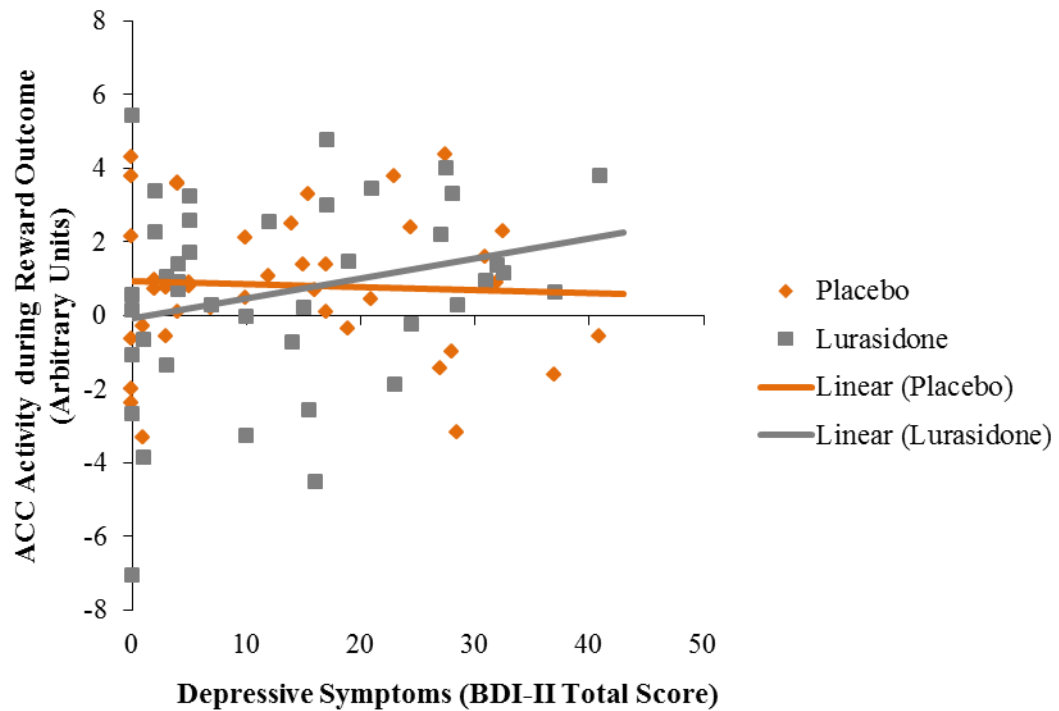


Figure 4.8. ACC response during Reward Outcome across continuous depression scores under lurasidone and placebo.

4.3.4.3 Secondary categorical analyses: using BDI-II cut-off scores

Complementing the primary (continuous variable) analyses, we sought to replicate our results using *categorical analyses*. A repeated-measures ANOVA with *Medication* (placebo, lurasidone) and *Outcome Type* (Reward Outcome versus Penalty Outcome) as the within-subject variables and *Depression Group* (low (BDI-II score: 0-16) versus high (BDI-II score: 17-43) depressive symptoms) and *Medication Order* as the between-subject factors ($n=40$), revealed a significant *Medication-by-Depression Group-by-Outcome Type* interaction in the ACC ($F(1,38)=8.68$, $p=.005$). However, this was not significant in the NAcc following Bonferroni correction ($F(1,38)=5.48$, $p=.025$).

Again, to understand the significant three-way interaction, we conducted two repeated-measures ANOVAs for *Reward Outcome* ($n=41$) and *Penalty Outcome* separately ($n=41$ after excluding outliers).

This revealed that the *Medication-by-Depression Group-by-Reward Outcome* interaction in the NAcc ($F(1,38)=6.63, p=.014$) and ACC ($F(1,38)=5.06, p=.031$) that fell short of significance after Bonferroni correction. Nevertheless, for visualisation purposes, Figure 4.9 and Figure 4.10 illustrate these findings using depression severity cut-off scores from the BDI-II and post-hoc tests using BDI-II cut-off scores as a grouping variable.

These post-hoc t-tests showed that participants with high depressive symptoms receiving lurasidone had significantly greater NAcc activation to *Reward Outcomes* than participants with low depressive symptoms receiving lurasidone ($t(38)=2.49, p=.017$). Figure 4.9 shows that participants with high depressive symptoms receiving lurasidone had greater NAcc activation to *Reward Outcomes* than participants with high depressive symptoms receiving placebo and participants with low depressive symptoms receiving placebo, however these differences were not statistically significant. For ACC activation during reward outcome, post-hoc t-tests using BDI-II cut-off scores as a grouping variable demonstrated that lurasidone potentiated ACC activation in participants with high depression severity relative to placebo ($t(16)=2.44, p=.027$). There was also a significant difference between individuals low and high in depression severity on lurasidone ($t(39)=2.57, p=.014$).

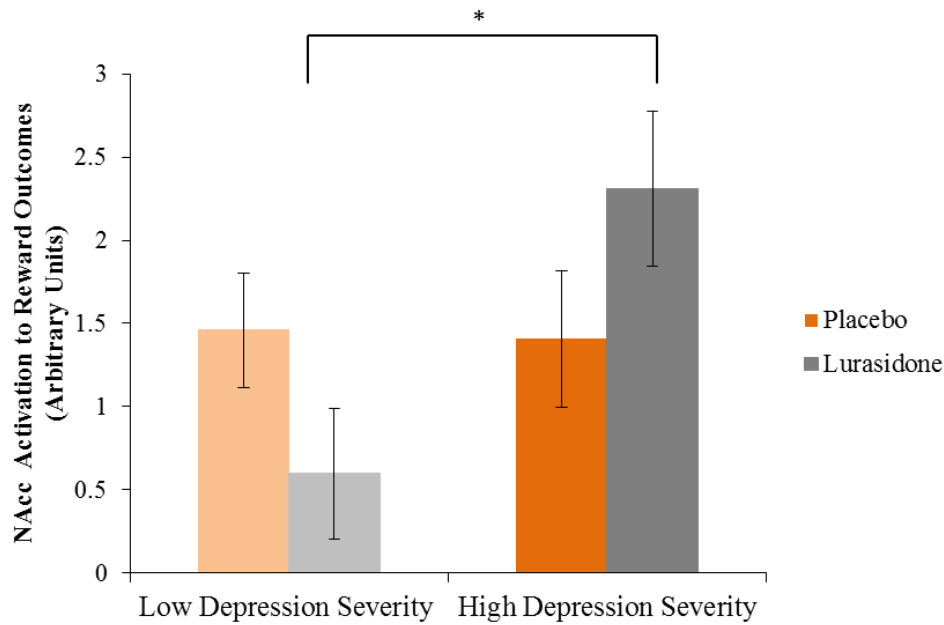


Figure 4.9. Nucleus Accumbens (NAcc) Response to Reward Outcomes (Win>Missed Win). Depression severity cut-off scores from the Beck's Depression Inventory-II, with individuals with low depressive symptoms (Total BDI-II score: 0-16, n=24) versus high depressive symptoms (Total BDI-II score: 17-43, n=18). Bars represent Standard Error.

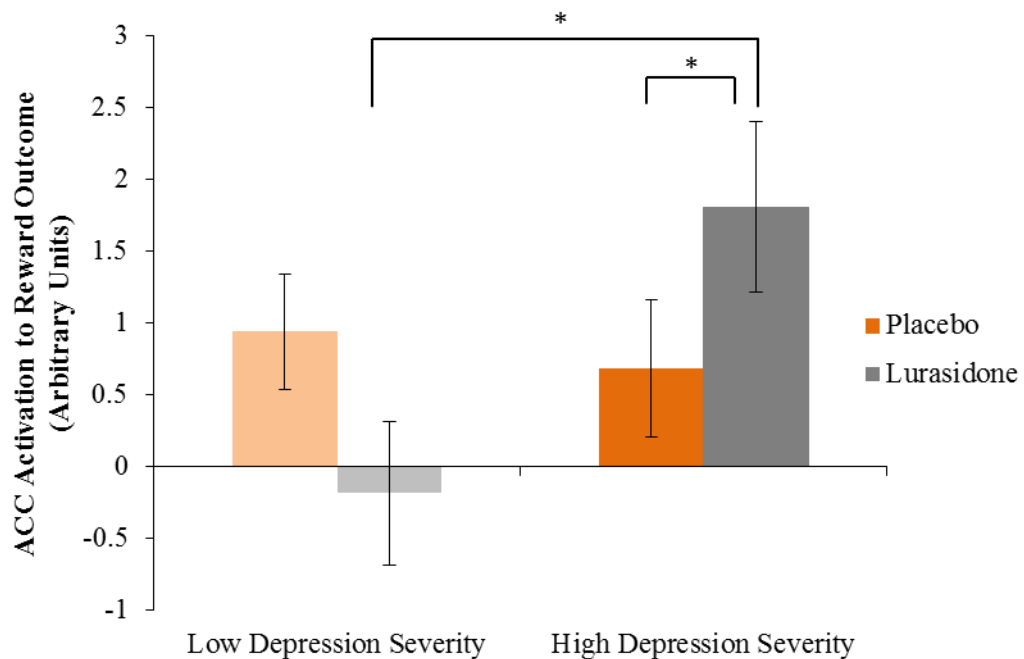


Figure 4.10. ACC response to Reward Outcomes (Win>Missed Win). Depression severity cut-off scores from the Beck's Depression Inventory-II, with individuals with low depressive symptoms (Total BDI-II score: 0-16, n=24) versus high depressive symptoms (Total BDI-II score: 17-43, n=18). Bars represent Standard Error.

4.3.4.4 Continuous analyses: using continuous anhedonia scores

We also examined whether there were any significant three way interactions with continuous scores of anhedonia, which could otherwise be concealed with the use of total depression severity scores, which combine various symptoms of depression. This was assessed with a repeated-measures ANCOVA for *Reward Outcome*⁸ with the inclusion of continuous anhedonia scores (SHAPS or DARS total score) as the covariate of interest. We found a modulation of reward-related outcome responses in the NAcc by lurasidone in individuals with more severe anhedonia scores as captured by the SHAPS: ($F(1,35)=7.93, p=.007$; passes Bonferroni correction); but not the DARS: ($F(1,35)=5.73, p=.022$). Figure 4.11 shows that under lurasidone, individuals with higher anhedonia scores had greater NAcc activity during reward outcomes. However, this trend was not found under placebo.

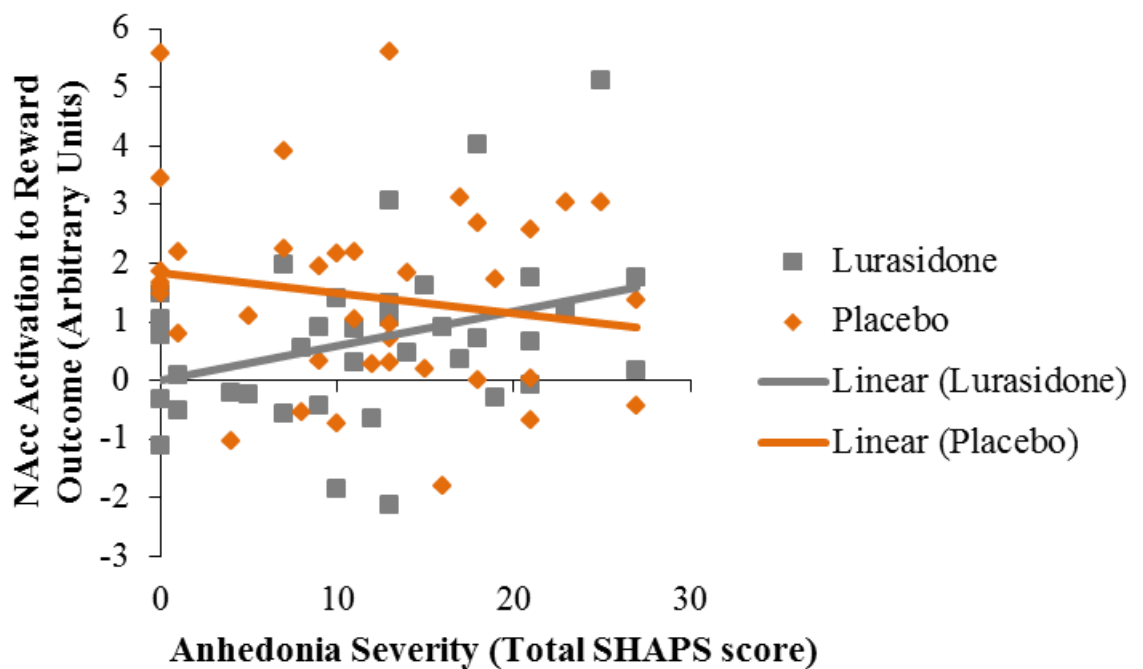


Figure 4.11. NAcc response during Reward Outcome across continuous anhedonia scores under lurasidone and placebo.

⁸ Unlike the analyses with depression severity, we did not use an omnibus model for the anhedonia analyses (i.e. using a within-subject variable Outcome Type (Reward outcome, penalty outcome), because our hypothesis for anhedonia was specific to positive feedback.

4.3.4.5 ***Test of Hypothesis 1d: Penalty Outcome.*** *Lurasidone will reduce the penalty-related feedback signal in the VS, ACC and insula. These effects will be most pronounced in individuals with higher depressive symptoms.*

4.3.4.6 ***Primary continuous analyses: using continuous depression symptoms scores***

As described in Section 4.3.4.1, the repeated measures ‘omnibus’ ANCOVA revealed a significant *Medication-by-Depression Severity-by-Outcome Type* interaction in the anterior cingulate cortex (ACC) ($F(1,37)=8.10, p=.007$). In this section we sought to understand this interaction by conducting a repeated-measures ANCOVA for *Penalty Outcome* separately.

These analyses revealed a significant *Medication-by-Depression Severity-by-Penalty Outcome* interaction in the ACC ($F(1,38)=11.98, p=.001$). Figure 4.12 demonstrates that under placebo, individuals with higher depressive symptoms had greater ACC activity during penalty outcomes. However, this trend was not found under lurasidone. Put simply, brain activity to penalties in the ACC in individuals with elevated depression scores under lurasidone, but not placebo, resembles brain activity of individuals with low depressive symptoms. In keeping with this result, we found that Δ ACC (the difference between neural activity under lurasidone and placebo) was negatively correlated with depression severity. Figure 4.13 illustrates the finding that the absolute difference in neural activity between lurasidone and placebo increased as a function of depression scores.

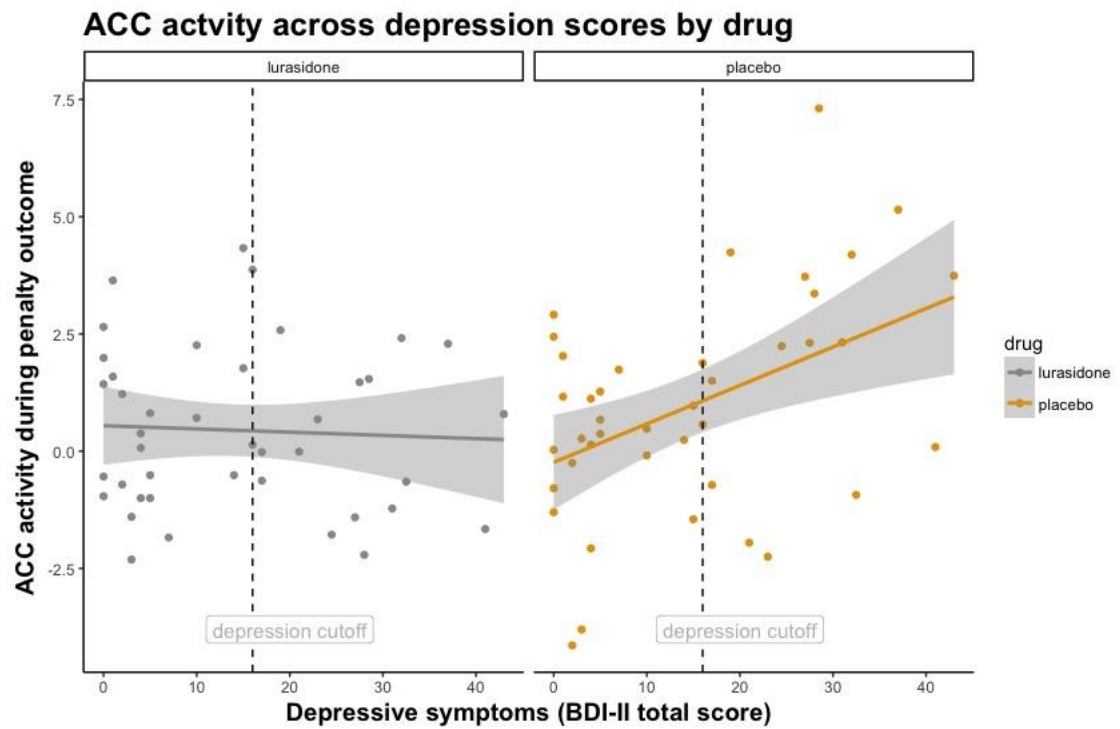


Figure 4.12. Facet plot illustrating ACC response during Penalty Outcome across continuous depression scores under lurasidone and placebo. Dashed vertical line denotes depression severity cut-off score on the Beck's Depression Inventory-II.

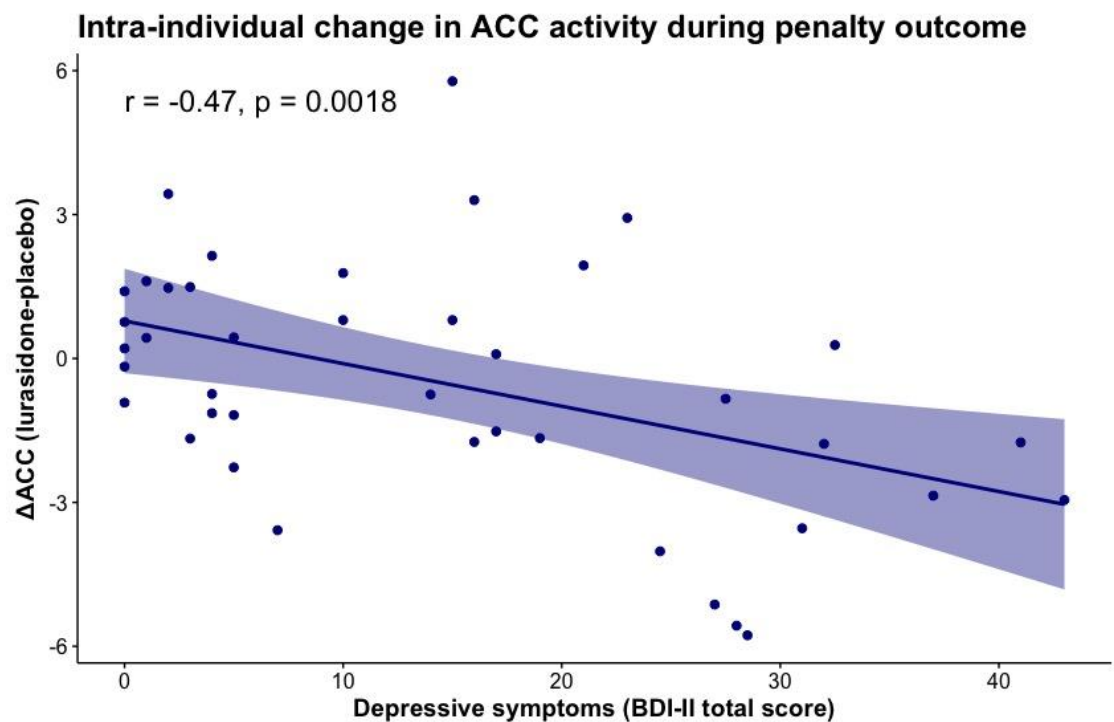


Figure 4.13. Intra-individual change in penalty-related ACC activity (the difference between neural activity under lurasidone and placebo) as a function of continuous depression scores.

A similar pattern of results, namely a signal normalisation, was found in the OFC ($F(1,37)=4.94, p=.032$), but the interaction fell short of significance after Bonferroni adjustment.

Although anhedonia was not hypothesised to be associated with penalty outcomes, for the sake of a comprehensive overview, we completed an exploratory analysis with a repeated-measures ANCOVA for *Penalty Outcome* with the inclusion of continuous anhedonia scores (SHAPS or DARS total score) as the covariate of interest. We found no significant main effects or interactions (all p values $> .050$).

4.3.4.7 ***Secondary categorical analyses: using BDI-II cut-off scores***

Complementing the primary (continuous variable) analyses, we sought to replicate our results using *categorical analyses*. As described in Section 4.3.4.1, the repeated measures ‘omnibus’ ANOVA revealed a significant, revealed a significant *Medication-by-Depression Group-by-Outcome Type* interaction in the ACC ($F(1,38)=8.68, p=.005$). In this section we sought to understand this interaction by conducting a repeated-measures ANOVA for *Penalty Outcome* separately.

This revealed that the *Medication-by-Depression Group-by-Penalty Outcome* interaction was significant in the ACC ($F(1,37)=8.15, p=.007$). Figure 4.14 illustrates these findings using BDI-II cut-off scores, with individuals with low depressive symptoms (Total BDI-II score: 0-16, $n=24$) versus high depressive symptoms (Total BDI-II score: 17-43, $n=18$). Post-hoc t -tests showed that participants with high depressive symptoms receiving placebo had significantly greater ACC activation to *Penalty Outcomes* than participants with high depressive symptoms receiving lurasidone ($t(19)=2.17, p=.043$), and participants with low depressive symptoms receiving placebo ($t(37)=2.32, p=.026$). There was no significant difference between individuals with high BDI-II scores on lurasidone and individuals with low BDI-II scores on placebo ($t(37)=0.48, p=.634$). Together, these findings indicate that brain activity to penalties in the ACC in individuals with elevated depression scores under lurasidone, but not placebo, resembles brain activity of healthy volunteers.

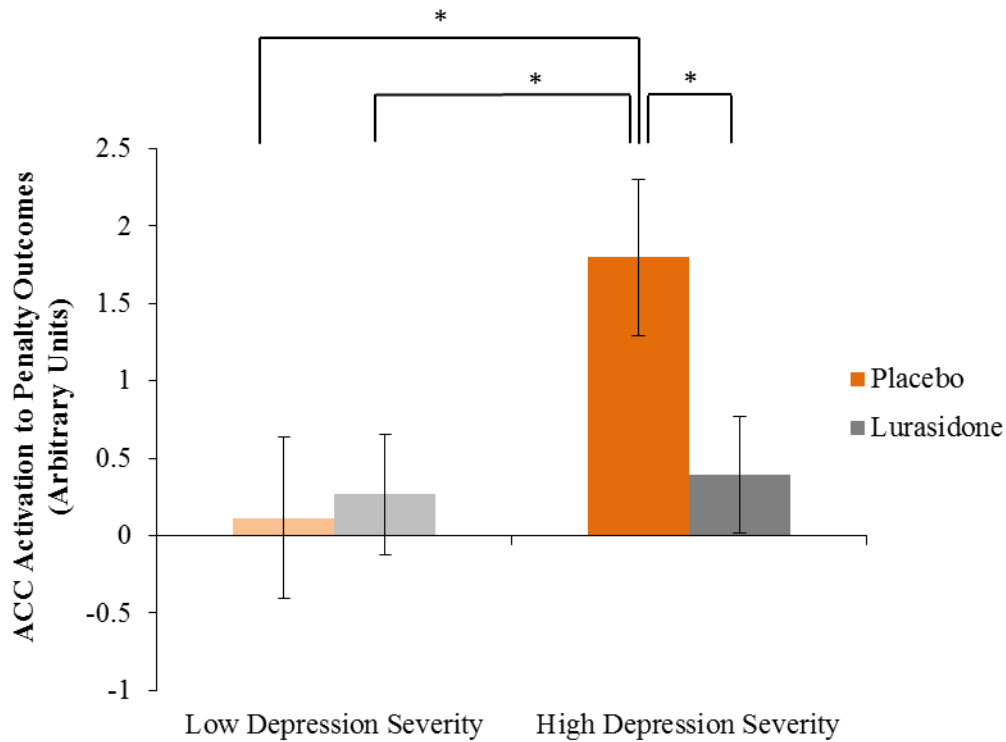


Figure 4.14. Box Plot illustrating ACC Response to Penalty Outcomes (Loss>Avoided Loss). Depression severity cut-off scores from the Beck's Depression Inventory-II, with individuals with low depressive symptoms (Total BDI-II score: 0-16, n=24) versus high depressive symptoms (Total BDI-II score: 17-43, n=18).

4.3.5 Sensitivity analysis: Inclusion of outliers (two subjects)

All analyses for responses to outcomes were repeated including the two participants with outlier values and all results remained the same. First, including outlier values in the repeated measures ANCOVA (n=42 instead of n=40), did not change the pattern or significance of the *Medication-by-Depression Severity-by-Outcome Type* interaction in the ACC, OFC and insula, according to the Bonferroni-corrected significance threshold ($p < .007$): ACC ($F(1,39)=12.99, p=.001$), orbitofrontal cortex (OFC) ($F(1,39)=4.51, p=.040$) and Insula ($F(1,39)=4.75, p=.035$). Second, the pattern or significance of the *Medication-by-Depression Severity-by-Penalty Outcome* interaction in the ACC and OFC remained the same (without outlier: ACC ($F(1,38)=11.98, p=.001$); OFC ($F(1,37)=4.94, p=.032$); with outlier: ACC ($F(1,39)=13.69, p=.001$) OFC ($F(1,39)=6.83, p=.013$)). Third, the *Medication-by-Depression Severity-by-Reward Outcome* interaction did not change (without outlier:

the NAcc ($F(1,38)=4.87, p=.033$) and ACC ($F(1,37)=5.92, p=.020$); with outlier: NAcc ($F(1,39)=5.65, p=.022$) and ACC ($F(1,39)=7.32, p=.010$).

4.3.6 Summary of outcome phase results

To summarise, across reward and penalty outcomes, lurasidone had its strongest effect of increasing responses to reward outcomes and decreasing responses to penalty outcomes in individuals with high depression severity (Figures 4.9 to 4.13). This pattern was statistically significant for penalty outcomes in the ACC, but fell short of significance for reward outcomes in the ACC and NAcc. Instead, we found a significant effect of medication on reward outcomes with respect to anhedonia symptoms. We found that lurasidone significantly increased NAcc activation in individuals with higher symptoms of anhedonia. The pattern and significance of all these results remained when the outliers were included in the analysis.

Table 4.4. Summary of continuous and categorical analyses for reward and penalty outcomes. Results surviving Bonferroni correction for multiple ROI comparisons ($p<.007$) are highlighted in bold.

Analysis type	Model	Medication-by-Depression- ROI Activation Interaction Result
Primary Continuous Analysis	Omnibus ANCOVA (Outcome Type: Reward and penalty outcome)	<ul style="list-style-type: none"> • ACC $p=.007$ ✓ • NAcc $p=.044$ ✗ • OFC $p=.041$ ✗ • Insula $p=.033$ ✗
	ANCOVA: Reward Outcome	<ul style="list-style-type: none"> • ACC $p=.020$ ✗ • NAcc $p=.033$ ✗
	ANCOVA: Penalty outcome	<ul style="list-style-type: none"> • ACC $p=.001$ ✓
	Omnibus ANOVA (Outcome Type: Reward and penalty outcome)	<ul style="list-style-type: none"> • ACC $p=.005$ ✓ • NAcc $p=.025$ ✗
	ANOVA: Reward Outcome	<ul style="list-style-type: none"> • ACC $p=.031$ ✗ • NAcc $p=.014$ ✗
	ANOVA: Penalty outcome	<ul style="list-style-type: none"> • ACC $p=.007$ ✓

4.3.7 **FMRI Whole-brain analysis for anticipation and outcome phases**

The aim of the whole brain analysis was to (i) test whether the task elicited the expected pattern of activation during reward and penalty anticipation and outcome (outside the effect of the drug) (Knutson et al., 2001) and (ii) model the effects of lurasidone and depression status beyond the fronto-striatal network targeted in the ROI analyses.

For the first aim, we found that whole-brain analyses across the entire sample on placebo ($n=42$) in response to anticipation and receipt of monetary rewards and penalties revealed the expected pattern of activation (Figure 4.15 and Figure 4.16).

Specifically, in response to reward anticipation and penalty anticipation, robust activation was observed across six common clusters including the striatum, ACC, cerebellum, precentral gyrus and motor preparation regions such as the supplementary motor area (cluster corrected to $p<.050$ by being required to exceed an extent of 626 and 614 continuous voxels for reward and penalty anticipation respectively, as determined by AFNI's 3DClustSim (Cox et al., 2017; Eklund et al., 2016b). Anticipation of rewards activated more dorsal regions of the caudate, whilst anticipation of penalties was more localised to the nucleus accumbens (ventral portion). Moreover, anticipation of losses additionally activated the insula and a portion of the amygdala (Figure 4.15).

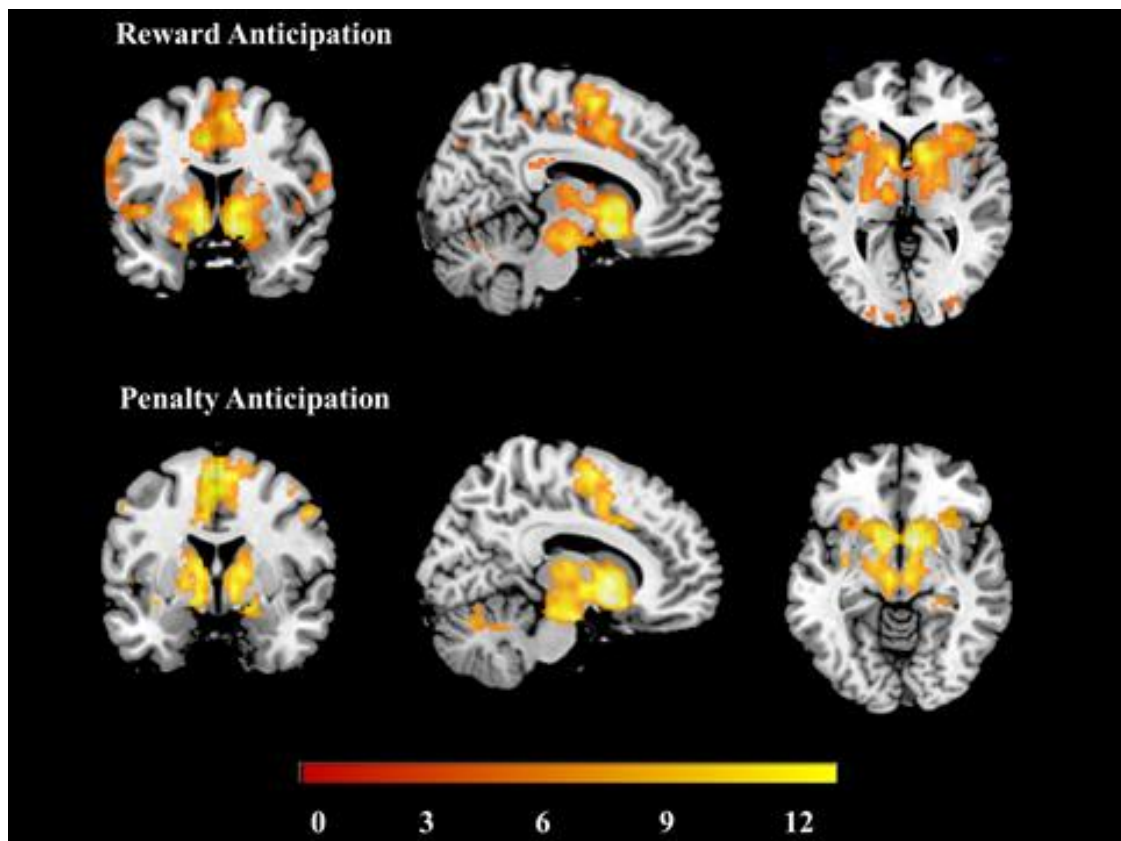


Figure 4.15. Whole-brain analyses across the entire sample on placebo ($n= 42$) in response to anticipation of rewards (top) and penalties (bottom). Reward anticipation elicited robust activation in the caudate (extending into NAcc and putamen), supplementary motor area, cerebellum, precentral gyrus and ACC. Penalty anticipation was associated with significant increases in activation in the NAcc, cerebellum, supplementary motor area, cerebellum, precentral gyrus, insula, ACC and amygdala. Cluster corrected to $p<.050$ by being required to exceed an extent of 626 and 614 contiguous voxels for reward and penalty anticipation respectively, as determined by AFNI's 3dClustSim (Cox et al., 2017; Eklund et al., 2016b). The image above is FWE-corrected to $p<.001$ for visualisation purposes. Bar represents T-values.

In response to receipt of monetary rewards participants exhibited significantly increased activity in bilateral ACC (cluster corrected to $p<.050$ by being required to exceed an extent of 56 continuous voxels in 3DClustSim). Penalty feedback activated an extended right lateralised cluster from the medial frontal gyrus to the frontal inferior orbital and middle temporal gyrus (cluster corrected to $p<.050$ by being required to exceed an extent of 111 continuous voxels in 3DClustSim).

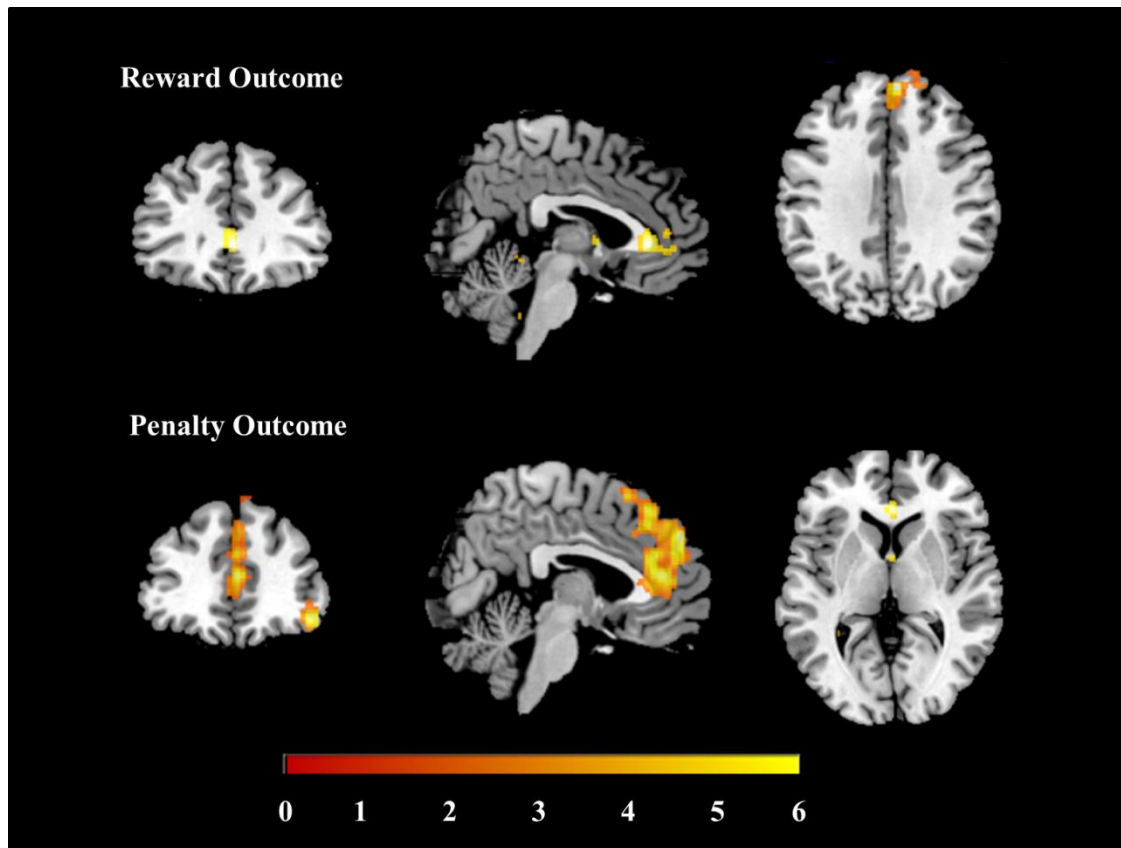


Figure 4.16. Whole-brain analyses across the entire sample on placebo ($n= 42$) in response to feedback of monetary rewards (top) and penalties (bottom). For visualisation purposes the image above is $p<.001$ (uncorrected). Bar represents T-values.

Overall, task-specific responses for reward/loss anticipation and outcome in the whole sample revealed the typical pattern usually observed in reward tasks including all ROIs which are known to be involved in the processing of reward and penalties (Pizzagalli et al., 2009a; Smoski et al., 2008; Ubl et al., 2015a).

Second, we used an independent samples t-test to explore the effects of lurasidone and depression status beyond the fronto-striatal network targeted in the analyses with the seven ROIs. The independent samples t-test demonstrated that there were no significant clusters or voxels for the interaction of *Medication*, *Medication Order* and all contrasts of interest. There were no significant associations between *Medication* and *Depression Severity* for the contrasts: (i) anticipation neutral>baseline (ii) anticipation win>baseline (iii) anticipation loss>baseline and (iv) feedback win>missed win. Using an un-corrected threshold, a cluster of 64 voxels in the ACC

($x=2, y=34, z=6, t=4.34, p=.046$) showed a positive correlation between depression severity and the contrast ‘feedback loss>avoided loss’ (placebo > lurasidone). However, this cluster did not survive the formal correction.

4.3.8 Prediction error

We next assessed the relationship between reward and penalty-related PE encoding and how these interacted with medication and depression severity. As explained in Methods Section 3.8.3.2 and 3.8.4.2, this analysis involved a repeated measures ANCOVA, where the within-subject variables included both types of PE (*PE Type*: Reward PE, Penalty PE) and *Medication* (placebo, lurasidone), the between-subject factor included *Medication Order* (placebo-lurasidone, lurasidone-placebo) and *Depression Severity* (total BDI score) score was the covariate of interest. We tested this in the three models (i) *Fixed PE Model*; (ii) *Dynamic PE model for all cues combined*; (iii) *Dynamic PE model for wins and penalty cues separately* (please see Methods Section 3.8.3.2 for model descriptions).

Across all three PE models we did not find any significant *Medication-by-Depression Severity-by-PE Type* interactions according to the Bonferroni correction (*Fixed PE Model*: amygdala, ($F(1,38)=7.04, p=.012$); *Dynamic PE model for all cues combined*: amygdala, ($F(1,38)=6.58, p=.015$); *Dynamic PE model for wins and penalty cues separately*: amygdala, ($F(1,38)=5.25, p=.028$)).

The reward and penalty PE may not be symmetrical because the action required in the reward condition is an approach behaviour for gain and in the penalty condition it is approach behaviour for loss avoidance. Thus, the PE for reward trials and penalty trials may not be equivalent. We therefore examined reward and penalty-related PE in separate ANCOVA models.

4.3.9 Test of Hypothesis 2a: Reward-related Prediction Error.

Lurasidone will alter (increase or decrease) the reward-related PE signal in the striatum, OFC and ACC. These effects will be most pronounced in individuals with higher depressive symptoms.

When we completed the ANCOVA for Reward-related PE, we found a significant *Medication-by-Depression Severity-by-Reward PE* interaction in the amygdala for the *Fixed PE model* only ($F(1,37)=11.94, p=.001$). This is plotted in Figure 4.17 and shows that that under lurasidone, individuals with higher depressive symptoms had stronger reward PE encoding in the amygdala. However, this trend was not found under placebo.

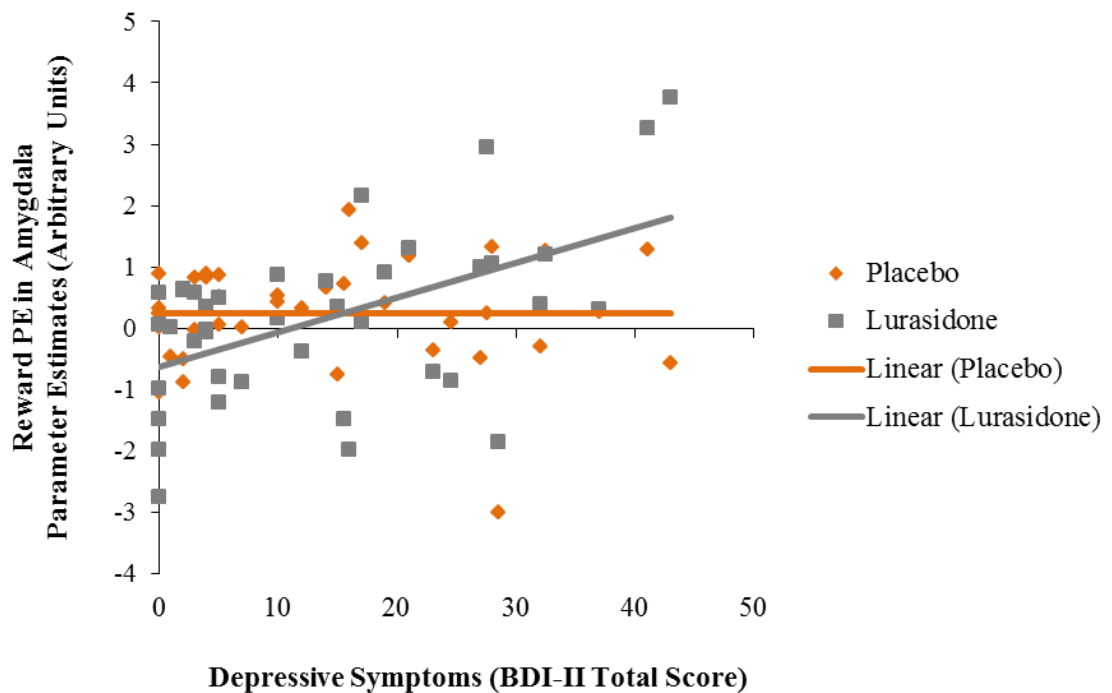


Figure 4.17. Encoding of win-related PE in the amygdala in the Fixed PE model

As mentioned above, there were no significant three-way interactions for the two dynamic models once the Bonferroni adjustment was applied: *Dynamic PE model for all cues combined*: OFC, $F(1,38)=5.21, p=.028$; Insula, $F(1,38)=4.39, p=.043$ and *Dynamic PE model for wins and penalty cues separately*: Amygdala, $F(1,38)=7.59, p=.009$; ACC, $F(1,38)=6.07, p=.018$; Insula, $F(1,38)=6.43, p=.016$; OFC, $F(1,38)=6.42, p=.016$; and Putamen, $F(1,38)=6.83, p=.013$.

4.3.10 Test of Hypothesis 2b: Penalty-related Prediction Error.

Lurasidone will alter (increase or decrease) the penalty-related PE signal in frontal, striatal and limbic regions: VS, ACC, amygdala and insula. These effects will be most pronounced in individuals with higher depressive symptoms.

We next examined penalty-related encoding, and found again, that the only significant results for an alteration in PE encoding as a function of drug and depression severity, was in the ACC for the *Fixed PE model*. As illustrated in Figure 4.18, individuals with higher depressive symptoms under placebo had higher (more negative) encoding of penalty PEs in the ACC and this trend was not found under lurasidone. Put simply, encoding of penalty-related PE in the ACC of individuals with elevated depression scores under lurasidone, but not placebo, resembled brain activity of individuals with low depressive symptoms.

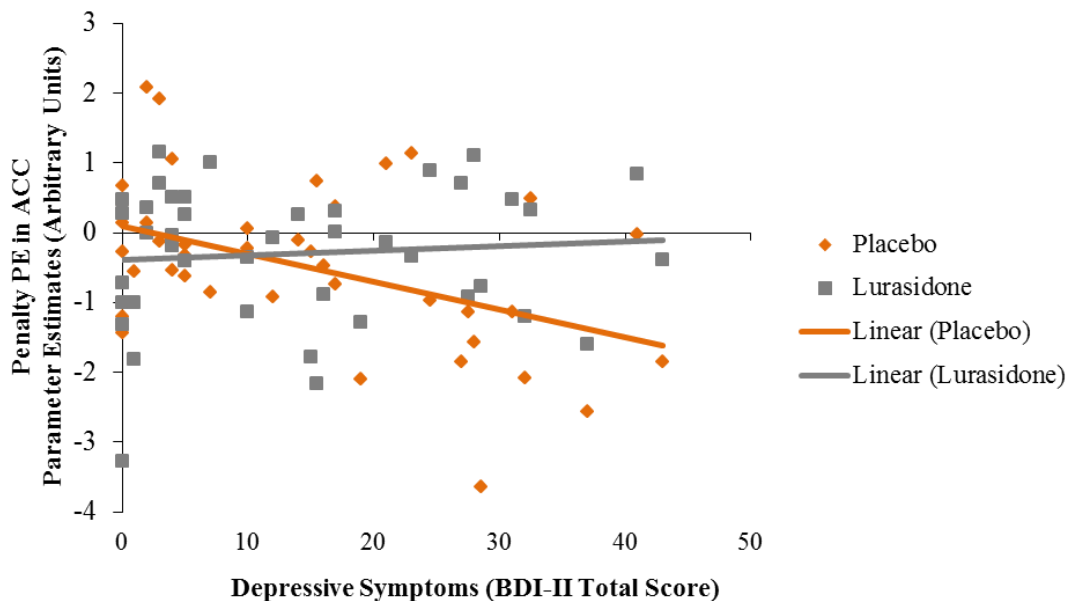


Figure 4.18. Encoding of penalty-related PE in the ACC in the Fixed PE model

In comparison to the *Fixed PE model*, the dynamic models did not show the same result, with a non-significant interaction in the amygdala for the *Dynamic PE model* for all cues combined (Amygdala, $F(1,38)=5.01$, $p=.032$), and no significant findings in the *Dynamic PE model* for wins and penalty cues separately.

We also completed an exploratory analysis to test the association between PE and anhedonia. This analysis was completed with the aim to elaborate on the findings for hypothesis 1c (significant increases in NAcc signalling to positive feedback with increasing anhedonia). We aimed to address the question: is lurasidone boosting pleasure experience or reward-related encoding in individuals with elevated anhedonia. The latter explanation would be supported by a significant *Medication-by-reward-related PE-anhedonia severity* interaction in the NAcc. However, a repeated-measures ANCOVA for *reward and penalty-related PE* with the inclusion of continuous anhedonia scores (SHAPS or DARS total score) as the covariate of interest showed no significant main effects or interactions (all p values > .050) across all three types of PE model.

4.3.11 Summary of Prediction Error results

To summarise, we found support for an alteration in reward-related PE encoding in the amygdala and penalty-related PE encoding in the ACC in only one of the three PE models, namely, the *Fixed PE model*. The other models did not show alteration in PE encoding after Bonferroni correction for multiple ROI comparisons (see Table 4.5). The pattern of results was one in which reward-related PE encoding (in the amygdala) remained equal across the range of depression severity, with lurasidone having opposite effects on encoding in subjects with lower versus higher depressive symptoms. On the contrary, encoding of penalty-related PE in the ACC of individuals with elevated depression scores under lurasidone, but not placebo, resembled brain activity of individuals with low depressive symptoms. This ‘normalisation’ effect seems to be a mirror of the results found for ACC activation to penalty outcomes (see Section 4.3.4.5).

Table 4.5. Summary of Medication-by Depression Severity-by-PE results used to test hypotheses 2a and 2b. Results surviving Bonferroni correction for multiple ROI comparisons ($p < .007$) are highlighted in bold.

PE Model Type/ Analytical model	Omnibus ANCOVA	Reward-related PE ANCOVA	Penalty-related PE ANCOVA
Fixed PE Model	<ul style="list-style-type: none"> Amygdala $F(1,38)=7.04, p=.012$ ✗ 	<ul style="list-style-type: none"> Amygdala $F(1,37)=11.94, p=.001$ ✓ 	<ul style="list-style-type: none"> ACC $F(1,38)=8.36, p=.006$ ✓ OFC $F(1,38)=4.72, p=.036$
Dynamic PE model for all cues combined	<ul style="list-style-type: none"> Amygdala $F(1,38)=4.66, p=.037$ ✗ 	<ul style="list-style-type: none"> OFC $F(1,38)=5.21, p=.028$ ✗ Insula $F(1,38)=4.39, p=.043$ ✗ 	<ul style="list-style-type: none"> Amygdala $F(1,38)=5.01, p=.032$ ✗
Dynamic PE model for wins and penalty cues separately	<ul style="list-style-type: none"> Amygdala $F(1,38)=6.51, p=.015$ ✗ 	<ul style="list-style-type: none"> Amygdala $F(1,38)=7.59, p=.009$ ✗ ACC $F(1,38)=6.07, p=.018$ ✗ Insula $F(1,38)=6.43, p=.016$ ✗ OFC $F(1,38)=6.42, p=.016$ ✗ Putamen $F(1,38)=6.83, p=.013$ ✗ 	<ul style="list-style-type: none"> N.s. findings ✗

4.3.12 Brain regions encoding PE: further ROI and whole brain analyses

We also conducted a ROI (small volume correction) analysis in SPM for each ROI separately to determine which ROIs (caudate, putamen, NAcc, OFC, ACC, insula and amygdala) encoded win- and penalty-related PE. This was done for the whole sample across both drugs across the three models.

As shown in Table 4.6, we found that the three types of PE model showed good overlap in terms of the brain regions encoding reward and penalty-related PE. The regions encoding reward-related PE in the *Fixed PE model* included the striatum (bilateral caudate, putamen and NAcc), ACC and amygdala. In comparison, penalty-related PE was also encoded in the OFC, but not in the ACC. The *Dynamic PE model*

for all cues combined seems to be the most sensitive model as it had the most number of regions encoding reward and penalty-related PE: striatum, ACC, amygdala, OFC and insula. For the *Dynamic PE model for wins and penalty cues separately*, the striatum and OFC encoded both reward and penalty PEs, whilst the insula and amygdala were only associated with loss-related PEs. An unexpected result across all three models was that whilst reward-related PE was encoded in the ACC, there was no evidence of penalty-related PE in the ACC.

Table 4.6. Regions of Interest (small volume correction) showing reward (n=80) and penalty-related (n=84) prediction error encoding in the entire sample on lurasidone and placebo.

Region	Peak MNI Coordinates ^a				
	x	y	z	T score	p-value ^b
<i>Fixed PE Model</i>					
Reward-related PE					
Right Caudate	14	14	-6	6.8	<.001
	21	6	21	4.79	.002
	20	2	23	4.74	.002
	20	-6	24	4.65	.003
	20	18	17	3.97	.022
	20	23	14	3.88	.029
	21	26	11	3.77	.040
Left Caudate	-14	15	-8	6.71	<.001
	-15	15	-3	6.22	<.001
	-11	24	0	4.55	.004
	-18	6	23	5.44	<.001
	-21	-20	24	4.47	.005
	-18	21	12	3.9	.027
Right Putamen	21	12	-8	7.38	<.001
	15	14	-6	6.81	<.001
	27	3	9	4.27	0.009
	27	-8	12	4.10	0.015
Left Putamen	-17	11	-9	7.53	<.001
Right Nucleus Accumbens	18	6	-12	5.21	<.001
	14	8	-8	4.54	<.001
	8	8	-8	3.34	.014
Left Nucleus Accumbens	-15	6	-11	5.85	<.001
	-15	8	-8	5.44	<.001
Right Anterior Cingulate Cortex	3	35	12		.004
				4.57	
	3	47	2	3.96	.027
	5	42	-3	3.95	.028

	8	32	-2	3.88	.034
	-5	41	5	3.82	.040
Left Anterior Cingulate Cortex	-5	54	0	6.21	.001
	-8	48	-5	6.04	.001
	-6	42	-6	5.07	.014
Right Amygdala	24	2	-12	3.93	.007
	20	5	-17	3.32	.040
Penalty-related PE					
Right Caudate	17	15	-6	6.55	<.001
	21	2	23	5.55	<.001
	21	18	17	5.11	.001
	21	12	18	5.01	.001
	20	23	14	4.84	.001
	21	26	11	4.36	.007
	23	21	3	3.97	.024
Left Caudate	-15	15	-8	6.85	<.001
	-15	15	-3	4.96	.001
	-14	9	23	5.73	<.001
	-20	3	21	5.57	<.001
	-12	23	11	5.03	.001
	-17	23	14	4.73	.002
	-14	20	14	4.57	.004
	-21	-15	24	4.48	.005
	-20	-24	23	4.11	.016
	-18	-8	24	3.87	.032
Right Putamen	23	14	-6	7.82	<.001
	29	3	0	6.27	<.001
	27	2	8	6.26	<.001
	30	-9	2	6.01	<.001
Left Putamen	-23	12	-5	8.15	<.001
	-24	3	9	6.48	<.001
	-27	-5	8	6.1	<.001
	-29	-12	6	5.87	<.001
Right Nucleus Accumbens	17	6	-11	5.34	<.001
	14	8	-8	3.62	.006
Left Nucleus Accumbens	-17	6	-2	6.03	<.001
	-15	8	-8	5.04	<.001
Right Orbital Frontal Cortex	32	-39	18	4.31	.014
	36	-39	20	4.00	.037
Right Amygdala	29	0	-12	4.34	.002
	24	2	-12	3.94	.007
Left Amygdala	-24	0	-12	3.87	.009
Dynamic PE model for all cues combined					
Reward-related PE					
Right Caudate	16	12	-12	5.29	<.001
	16	16	-10	5.07	.001
	10	20	-8	4.04	.023

	20	4	20	4.6	.004
	20	-8	24	4.17	.016
	20	24	10	4.06	.022
Left Caudate	-18	20	8	4.28	.011
	-20	2	22	4.22	.014
	-18	12	16	4.31	.010
	-12	14	-12	3.89	.036
Right Putamen	20	14	-10	6.20	<.001
	28	-14	10	4.13	.018
Left Putamen	-20	14	-10	5.32	<.001
	-20	18	8	4.17	.016
Right Nucleus Accumbens	16	12	-14	5.56	<.001
Left Nucleus Accumbens	-16	10	-14	5.03	<.001
Right Orbital Frontal Cortex	18	14	-16	6.32	<.001
	32	-38	20	3.98	.045
Left Orbital Frontal Cortex	-16	14	-16	6.30	<.001
Right Anterior Cingulate Cortex	10	34	2	4.00	.032
Left Anterior Cingulate Cortex	-2	54	-2	5.29	<.001
	-4	42	2	4.63	.004
	-6	48	-4	4.11	.023
Left Insula	-24	10	-18	4.88	.003
Right Amygdala	20	6	-18	5.72	<.001
Left Amygdala	-24	4	-18	4.74	.001
Penalty-related PE					
Right Caudate	20	2	22	5.26	<.001
	18	24	12	4.72	.002
	20	18	16	4.28	.010
	18	14	20	4.26	.011
	20	26	6	4.18	.014
	14	14	-12	3.91	.032
Left Caudate	-16	6	22	5.38	<.001
	-20	-14	24	5.01	.001
	-18	-6	24	4.45	.006
	-12	22	10	5.15	.001
	-16	26	4	4.25	.011
Right Putamen	24	12	-10	5.3	<.001
	28	4	-8	5.02	.001
	30	0	-2	4.83	.002
	28	-6	8	4.72	.002
	30	-6	-2	4.46	.006
Left Putamen	-26	6	-6	4.86	.002
	-24	10	-10	4.85	.002
	-28	-12	2	4.71	.003
	-24	2	10	4.59	.004
	-26	6	2	4.58	.004
	-28	-8	8	4.54	.005
Right Nucleus Accumbens	12	12	-14	5.13	<.001
Left Nucleus Accumbens	-16	10	-14	4.68	<.001

Right Orbital Frontal Cortex	18	14	-16	5.18	.001
Left Orbital Frontal Cortex	-18	14	-14	5.07	.001
Left Insula	-26	8	-14	4.47	.010
	-24	10	-18	3.96	.050
Right Amygdala	28	0	-12	4.57	.001
	22	6	-18	4.42	.002
Left Amygdala	-26	2	-16	4.43	.002

Dynamic PE model for wins and penalty cues separately

Reward-related PE					
Right Caudate	20	22	2	4.14	.018
Left Caudate	-18	22	6	4.07	.023
	-16	20	-4	3.94	.033
	-12	24	-4	3.79	.050
	-18	6	22	3.92	.035
Right Putamen	22	16	-8	4.48	.006
	26	8	2	4.27	.012
	24	12	-2	4.2	.016
	20	18	2	3.86	.042
Left Putamen	-20	16	-8	4.49	.006
	-18	20	-4	4.22	.015
Right Nucleus Accumbens	16	14	-12	3.69	0.007
	12	12	-14	3.45	0.013
Right Orbital Frontal Cortex	18	14	-16		.006
				4.59	
Left Orbital Frontal Cortex	-18	14	-16	4.00	.043
Right Anterior Cingulate Cortex	10	34			
			0	4.41	.010
	0	34	8	4.23	.017
Left Anterior Cingulate Cortex	-4	40			
			2	4.68	.004
	-6	54	-2	4.08	.027
	-6	48	-4	3.88	.048
Penalty-related PE	20	2	22	4.99	.001
Right Caudate	18	20	14	4.42	.006
	20	22	-4	4.46	.005
Left Caudate	-18	6	20	4.91	.001
	-20	-18	24	4.75	.002
	-12	22	8	3.95	.026
	-16	26	2	3.84	.037
Right Putamen	30	-4	2	6.13	<.001
	24	14	-6	5.94	<.001
	30	0	-10	5.27	<.001
Left Putamen	-28	-12	2	6.04	<.001
	-26	4	2	5.79	<.001
	-24	16	-8	5.04	.001
Right Nucleus Accumbens	-16	10	-14	4.45	<.001

Left Nucleus Accumbens	16	12	-14	3.5	.010
Right Orbital Frontal Cortex	18	14	-14	4.12	.025
Left Orbital Frontal Cortex	-18	14	-16	4.71	.003
Left Insula	-26	8	-14	4.69	.004
Right Amygdala	30	-2	-12	4.99	<.001
Left Amygdala	-26	-2	-12	4.32	.002
	-26	2	-16	4.27	.003

a Montreal Neurological Institute coordinates.

b Significance at $p < .05$ (family-wise error-corrected for anatomical region of interest).
Region of Interests (ROIs) tested: Bilateral caudate, putamen, nucleus accumbens (NAcc), orbitofrontal cortex (OFC), anterior cingulate cortex (ACC), insula and amygdala

In addition to the ROI analyses of PE, we conducted a whole-brain analysis for the whole sample across both drugs (84 scans). The results are displayed in Figure 4.19 to Figure 4.21.

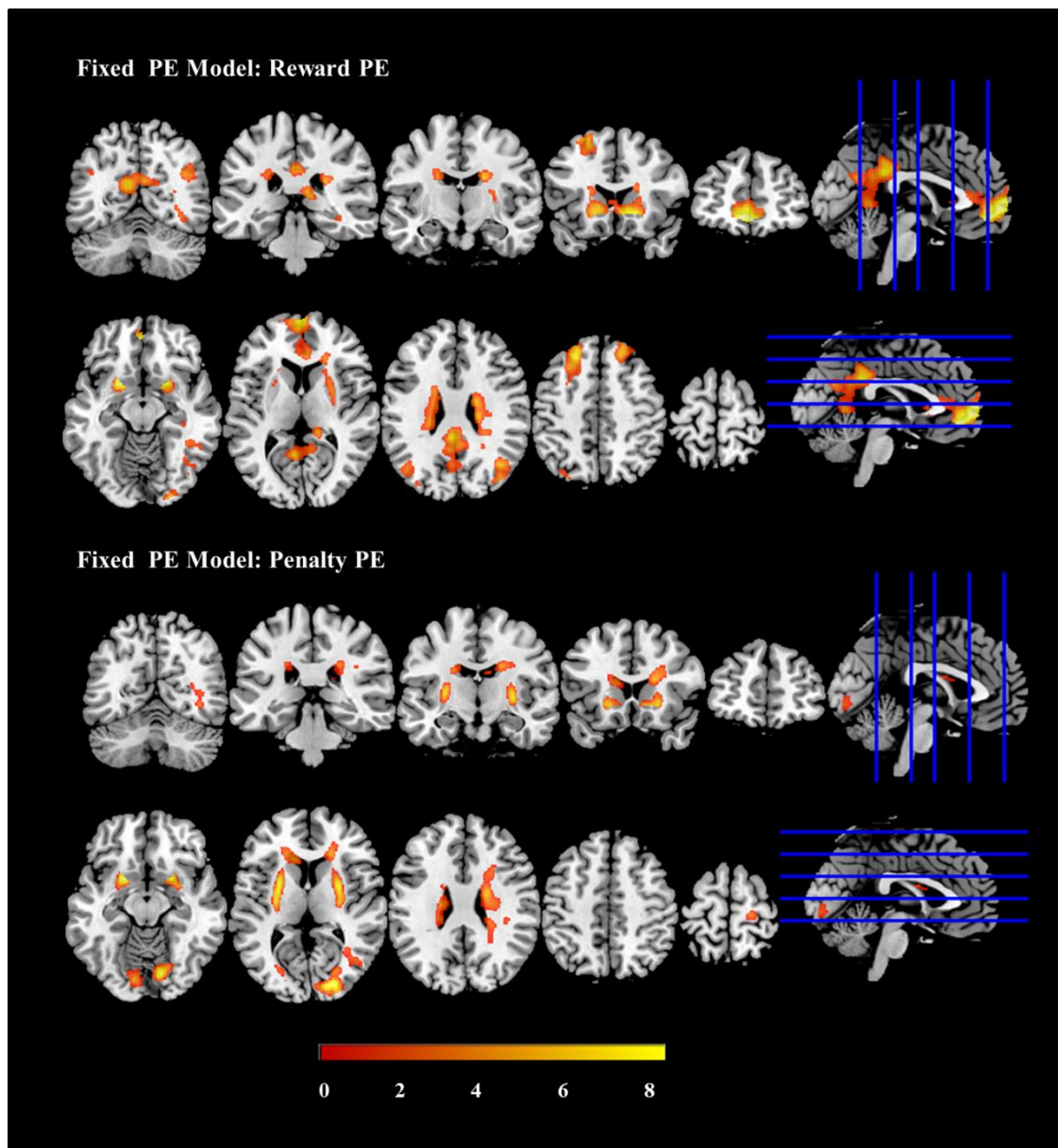


Figure 4.19. Whole-brain analyses showing regions of the brain that significantly encode reward (top) and penalty (bottom) related PE in the whole sample across placebo and lurasidone (n=84 scans) using the Fixed PE Model. Regions significantly encoding reward-related PE include R putamen, R lingual, bilateral frontal superior cortex, and bilateral occipital cortex. Regions significantly associated with penalty-related PE include bilateral putamen, lingual gyrus and precentral gyrus. Cluster corrected to $p < .050$ by being required to exceed an extent of 567 and 742 contiguous voxels for reward and penalty PE respectively, as determined by AFNI's 3dClustSim (Cox et al., 2017; Eklund et al., 2016b). Bar represents T-values.

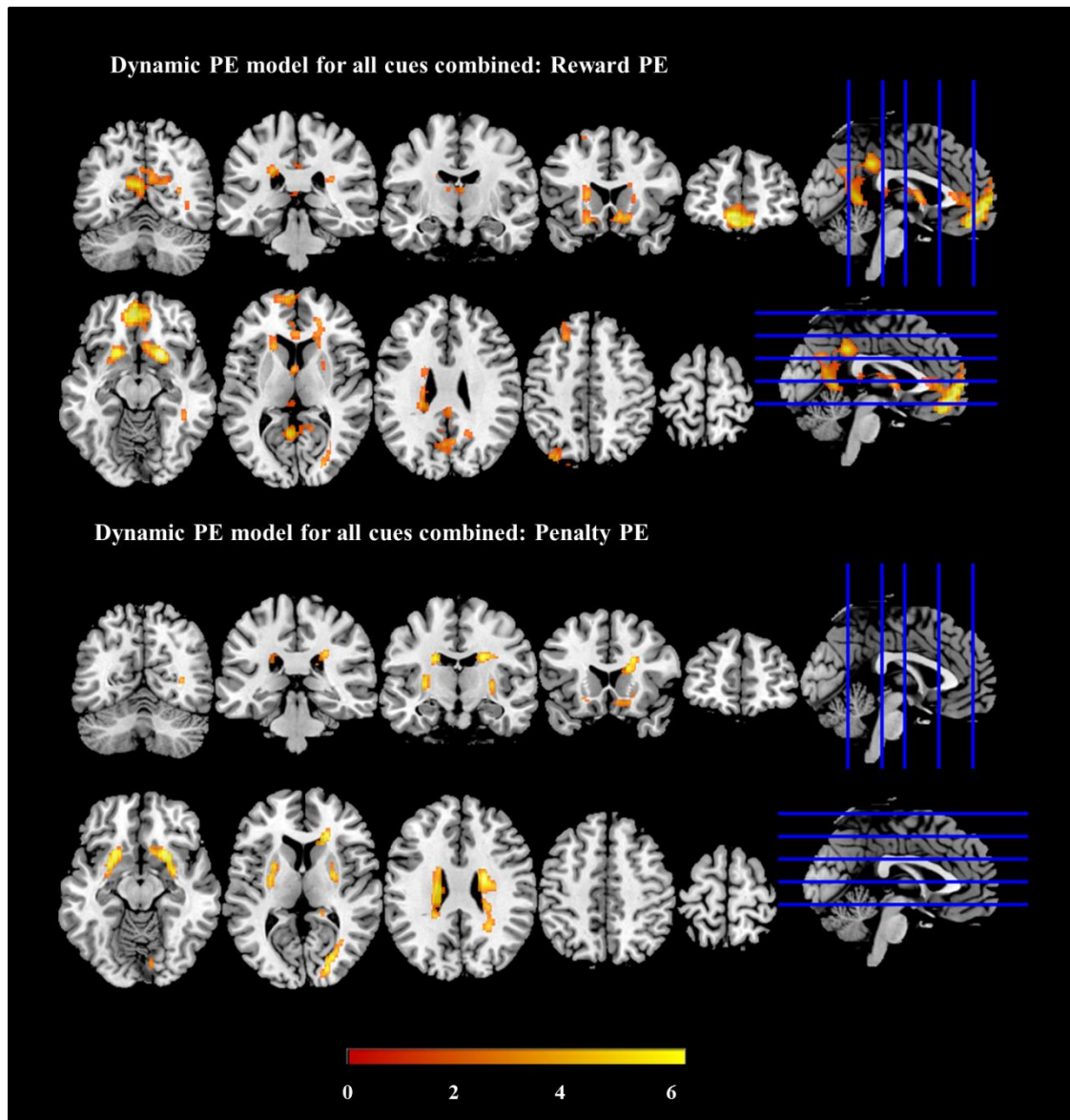


Figure 4.20. Whole-brain analyses showing regions of the brain that significantly encode reward (top) and penalty (bottom) related PE in the whole sample across placebo and lurasidone ($n=84$ scans) using the Dynamic PE model for all cues combined. Regions significantly encoding reward-related PE include posterior OFC, cingulate, occipital cortex, frontal superior cortex, hippocampus, caudate and medial PFC. Regions significantly associated with penalty-related PE include caudate, lingual gyrus, rectus and precuneus. Cluster corrected to $p<.050$ by being required to exceed an extent of 301 and 430 contiguous voxels for reward and penalty PE respectively, as determined by AFNI's 3dClustSim (Cox et al., 2017; Eklund et al., 2016b). Bar represents T-values.

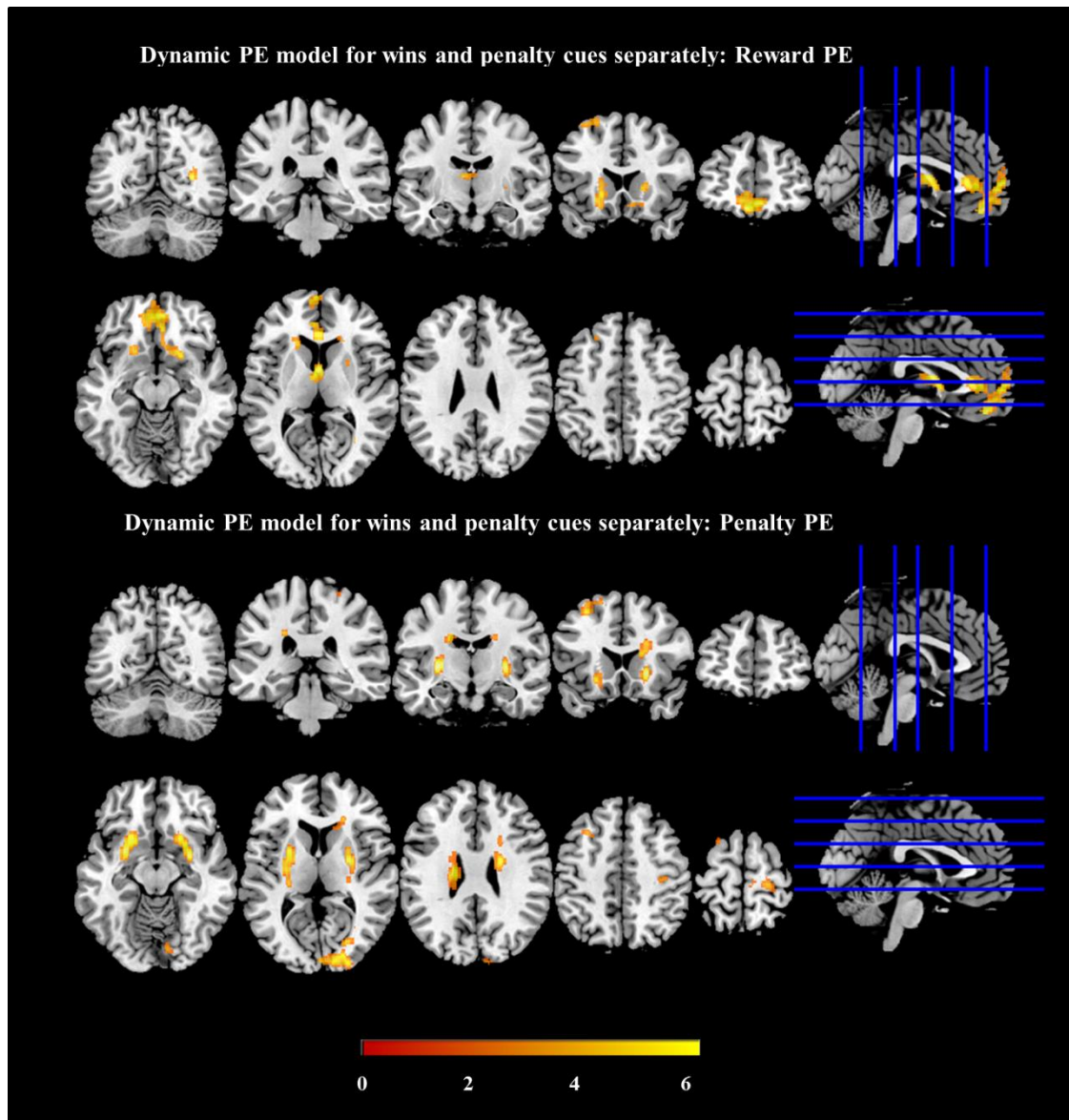


Figure 4.21. Whole-brain analyses showing regions of the brain that significantly encode reward (top) and penalty (bottom) related PE in the whole sample across placebo and lurasidone ($n=84$ scans) using the Dynamic PE model for wins and penalty cues separately. Regions significantly encoding reward-related PE include middle frontal cortex, calcarine, caudate, rectus, posterior OFC. Regions significantly associated with penalty-related PE include calcarine, bilateral putamen, R middle frontal cortex and R precentral cortex. Cluster corrected to $p<.050$ by being required to exceed an extent of 175 and 206 contiguous voxels for reward and penalty PE respectively, as determined by AFNI's 3dClustSim (Cox et al., 2017; Eklund et al., 2016b). Bar represents T-values.

4.3.13 Tests to validate the PE models

We completed additional analyses on the PE model to examine whether the penalty-related PE could be differentiated from the ACC activity during the error related trials (i.e. penalty feedback) per se. Indeed, a common issue for studies investigating the neural coding of PEs is the inherent correlation between PE trajectories and outcome magnitudes (Chowdhury et al., 2013a). This bears the risk that neural PE signals might be largely driven by the outcome magnitude alone. To address this issue, we correlated the extracted values from the ACC ROI for Penalty feedback (‘feedback loss>avoid loss’) and Penalty-related PE (penalty PE > baseline). They were highly correlated ($r=-.98$, $p<.001$ for both drugs across subjects) in the *Fixed PE model* and also significantly correlated in the *Dynamic PE model for all cues combined*. However, this was not the case for the other dynamic PE model.

Table 4.7. Correlation between extracted values from the ACC ROI for Penalty feedback (‘feedback loss>avoid loss’) and Penalty-related PE (penalty PE > baseline) across the three PE models: Fixed PE Model, Dynamic PE model for all cues combined, Dynamic PE model for wins and penalty cues separately.

	Fixed PE model		Dynamic PE model for all cues combined		Dynamic PE model for wins and penalty cues separately.	
	Penalty PE lurasidone (ACC)	Penalty PE placebo (ACC)	Penalty PE lurasidone (ACC)	Penalty PE placebo (ACC)	Penalty PE lurasidone (ACC)	Penalty PE placebo (ACC)
Penalty Feedback lurasidone (ACC)	r= -0.98, p<.001	r= 0.17, p=.285	r= -0.59, p<.001	r= -0.13, p=.414	r= -.16, p=.314	r= 0.05, p=.757
Penalty feedback placebo (ACC)	r= -0.19, p=.220	r= -0.98, p<.001	r= -.043, p=.789	r= -0.87, p<.001	r= -0.01, p=.979	r= 0.07, p=.692

We next correlated the penalty feedback regressor with the penalty PE regressor *within subject* across the fixed and dynamic PE models. As shown in Table 4.8 below, there were no significant correlations, and this remained when we combined runs 1 + 2 of the MID tasks for each drug (lurasidone run 1+2, placebo runs 1+2). Thus, collinearity was not an issue in any of the models. However, the result seemed odd given that both regressors were convolved with the HRF and we would therefore expect them to have a higher correlation than $r=0.004$.

Table 4.8. Correlation between penalty feedback regressor and penalty PE regressor in one subject across the fixed and dynamic PE models.

Correlation between penalty feedback regressor and penalty PE regressor	Fixed PE Model	Dynamic PE models
placebo MID run 1	$r=-0.004$, $p=.949$	$r=-0.002$, $p=.971$
placebo MID run 2	$r=-0.004$, $p=.957$	$r=0.002$, $p=.975$
lurasidone MID run 1	$r=-0.002$, $p=.980$	$r=0.001$, $p=.986$
lurasidone MID run 2	$r=0.000$, $p=.996$	$r=-0.007$, $p=.913$

In order to understand why these regressors were not correlated, we plotted the regressors for the *Fixed PE model* and the moving average (*Dynamic*) *PE model*.

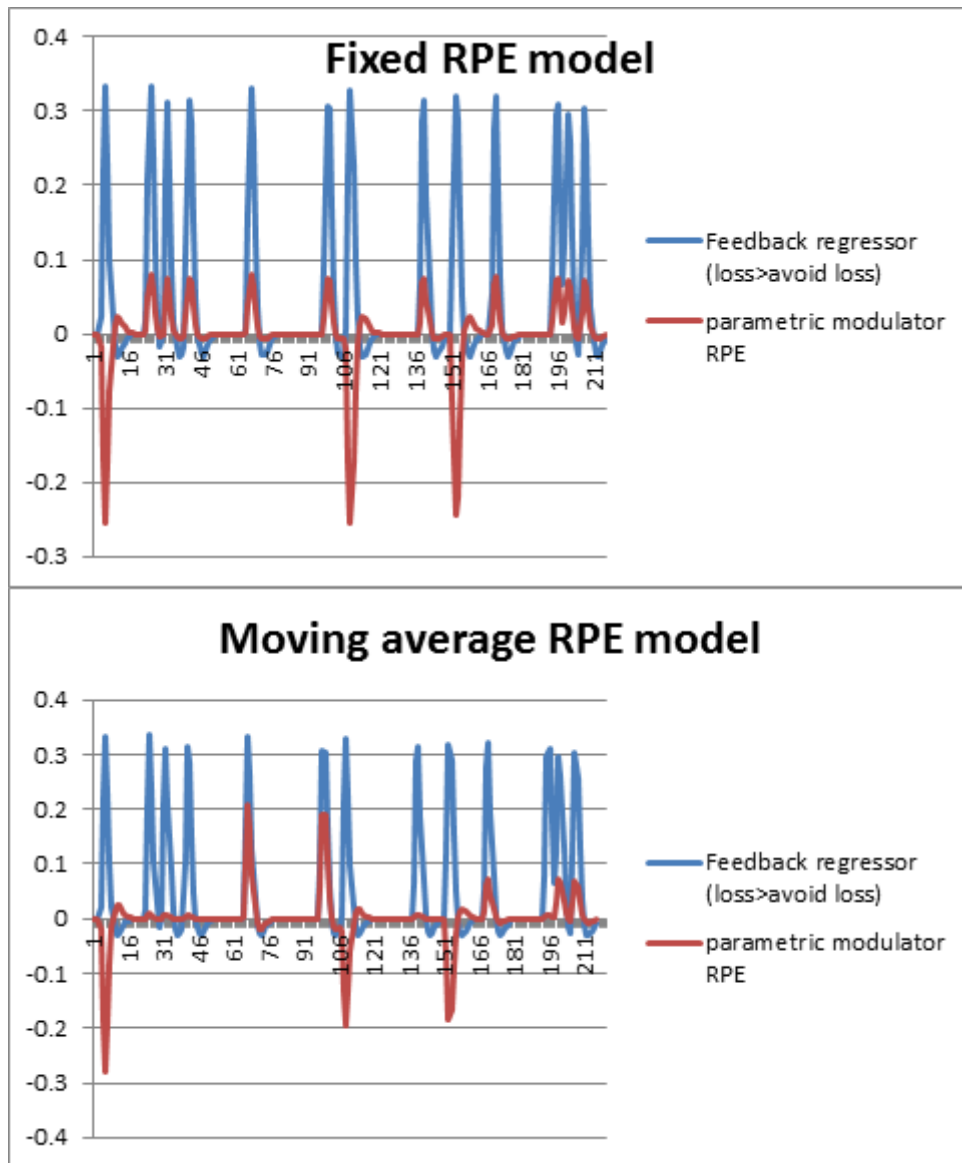


Figure 4.22. Plots showing correlations and anti-correlations between penalty feedback regressor and the Penalty-related PE regressor (parametric modulator) in one subject for the Fixed and Dynamic PE models.

The correlations may have been low between the feedback and parametric modulator PE regressor because, while the time series for errors is a simple event, the PE regressors are correlated (with the loss related) on some trials and anti-correlated at other time points. Thus, the dips in the red line cancel out the peaks in the blue line.

Taken together, the analyses above suggest that the PE signalling cannot be reliably distinguished from outcome magnitudes.

4.4 Sensitivity Analyses

The aim of these final set of analyses was to test the sensitivity or ‘fine-tune’ the predicted outcomes of hypotheses (1) and (2). This section thus aims to rule out a scenario in which the significant results described above are confounded by (a) comorbid anxiety symptoms; (b) self-reported changes in sedation and/or state-anxiety scores and (c) the predicted increase in baseline regional (striatal) CBF or shifts in global CBF under lurasidone relative to placebo in all participants.

4.4.1 **Test of Hypothesis 3a.** *Lurasidone’s effects on reward and penalty processing in depression will not be confounded by comorbid anxiety disorders.*

In order to test this hypothesis, we first tested for an association between dimensional anxiety scores and brain activation. If there were to be no association, then there would be no need to include it as a covariate in the depression severity ANCOVA models used in hypotheses 1a-2b above (as recommended by Miller and Chapman 2001).

A repeated measures ANCOVA was completed for the anticipation phase (*Cue Type* (Reward, Penalty, Neutral)) and outcome phase (*Outcome Type* (Reward Outcome versus Penalty Outcome)) of the task with *Medication* (placebo or lurasidone) as the within-subject factor, *Medication Order* (placebo-lurasidone, lurasidone-placebo) as the between-subject factor; and *Anxiety Severity* (total anxiety score from the HADS) as the covariate of interest. There were no significant associations between brain activity and anxiety and no significant interactions between *Medication*, *Anxiety Severity* and *Anticipation cue* in the ACC ($F(2,74)=0.01$, $p=.995$), Caudate ($F(2,74)=0.32$, $p=.727$), Putamen ($F(2,74)=0.58$, $p=.944$), Amygdala ($F(2,74)=0.64$, $p=.938$), OFC ($F(2,74)=0.05$, $p=.995$), NAcc ($F(2,74)=1.09$, $p=.341$), and Insula ROIs ($F(2,74)=0.13$, $p=.987$). There were also no significant three way interactions between *Medication*, *Anxiety Severity* and *Outcome Type* in the ACC ($F(1,37)=5.92$, $p=.020$), Amygdala ($F(1,37)=0.59$, $p=.449$), OFC ($F(1,37)=1.02$, $p=.319$), Caudate ($F(1,37)=2.82$, $p=.101$), Putamen ($F(1,37)=5.92$, $p=.020$), NAcc ($F(1,37)=0.08$, $p=.931$) and Insula ROIs ($F(1,37)=3.27$, $p=.079$) after Bonferroni correction for

multiple (seven) ROI comparisons. Therefore, anxiety severity was not included as a covariate in the ANCOVA model with depression severity (Miller and Chapman, 2001).

4.4.2 **Test of Hypothesis 3b.** *Lurasidone's effects on reward and penalty processing in depression will not be confounded by self-reported changes in sedation or state-anxiety scores.*

As described in Section 3.2.2, the effects of lurasidone on sedation and state-anxiety were measured at three time points: pre-scan, peak-of-drug and post-scan utilising the VAS and STAI-S questionnaires respectively. It is important to examine subjective ratings to exclude the possibility that any effects of lurasidone on behavioural/neural responses to rewards or penalties are secondary to an alteration in somnolence, alertness or tranquillity.

Thus, we examined the effect of *Medication*, *Medication Order* and *Depression Severity* on the change in *Sedation* ratings (Total Visual Analogue Scale (VAS) scores) and *State-anxiety* ratings (total STAI score) from pre-drug administration (Measure 1) to peak-of-drug (Measure 2). The change scores for these measures are shown in Table 4.3, Figure 4.23 and Figure 4.24. The repeated measures ANCOVA revealed that the interactions between *Medication* and *State-anxiety* ($F(1,37)=0.14$, $p=.708$) and interactions between *Medication* and *Sedation ratings* ($F(1,40)=0.20$, $p=.658$) were non-significant. There were no significant interactions with *Medication Order* (all p values > 0.05). Three way interactions between *Medication*, *Depression Severity* and *Sedation* ($F(1,40)=1.34$, $p=.253$), and, *Medication*, *Depression Severity* and *State-anxiety* ($F(1,40)=0.04$, $p=.480$) were also non-significant. These results suggest that lurasidone did not lead to a significant change in sedation or state anxiety relative to placebo over a period of three hours, and that this was consistent across the continuum of depression severity.

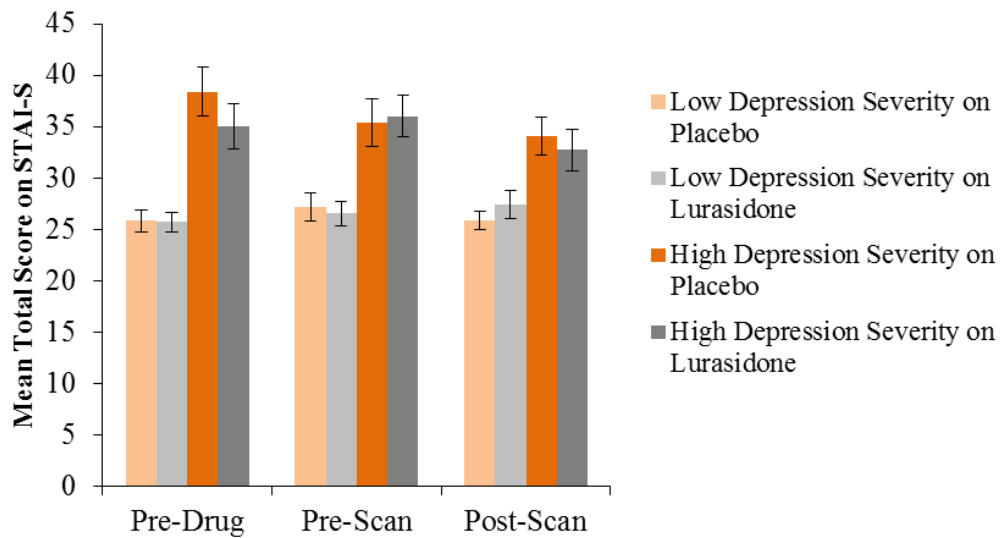


Figure 4.23. Effect of medication on State Anxiety Scores (STAI-S) by depression severity cut-off scores from the Beck's Depression Inventory-II: individuals with *low depressive symptoms* (Total BDI-II score: 0-16 (normal-mild mood disturbance), $n=24$) versus *high depressive symptoms* (Total BDI-II score: 17-43 (borderline-severe depression), $n=18$). The higher the score, the more anxious the participant felt. Error bars represent the standard error of the mean.

We then completed an additional analysis of the VAS in which the 16 scales of the VAS were reduced to two summary factors of Alertness and Tranquillity (Herbert et al., 1976) (see Methods Section 3.2.2 and Figure 4.24). The change in Alertness and Tranquillity ratings from pre-drug to peak-of-drug were then entered into the same repeated measures ANCOVA described above. For the alertness factor, we found no significant effect of *Medication* ($F(1,40)=0.12$, $p=.727$), *Medication Order* ($F(1,40)=1.15$, $p=.289$) or any interactions between these factors and *Depression Severity*. For the tranquillity factor, we also found no significant effect of *Medication* ($F(1,40)=0.20$, $p=.660$), *Medication Order* ($F(1,40)=1.57$, $p=.217$) or any interactions between these factors and *Depression Severity*.

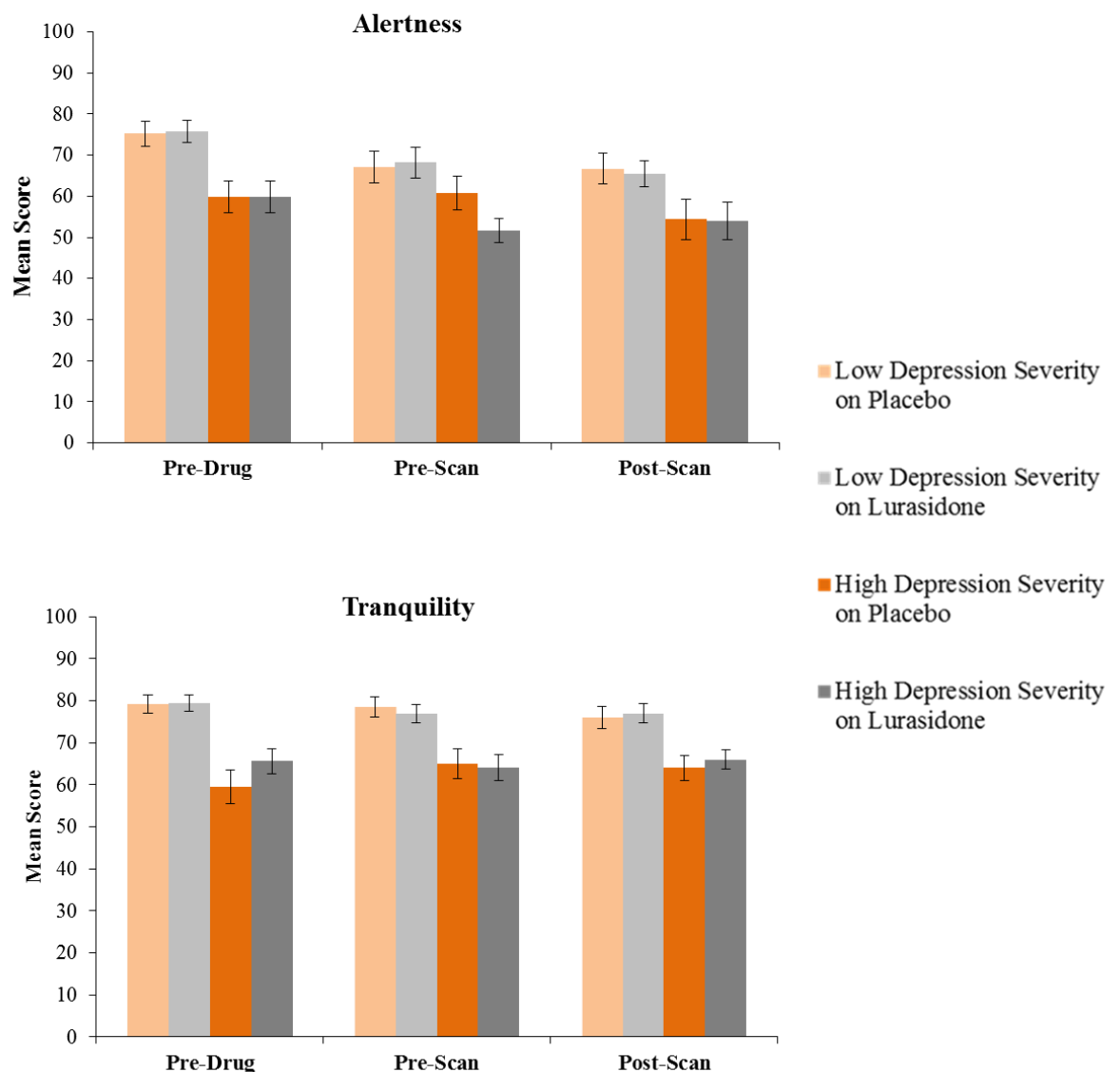


Figure 4.24. Effect of medication on the Visual Analogue Scale separated by Alertness and Tranquillity and depression severity cut-off scores from the Beck's Depression Inventory-II: individuals with low depressive symptoms (Total BDI-II score: 0-16 (normal-mild mood disturbance), n=24) versus *high depressive symptoms* (Total BDI-II score: 17-43 (borderline-severe depression), n=18). The higher the score, the more alert/tranquil the participant felt. Error bars represent the standard error of the mean.

Overall, we found no evidence that an acute dose of lurasidone alters subjective ratings of state anxiety, overall sedation scores, nor its subcomponent factors of alertness and tranquillity. Therefore, there was no need to include subjective ratings as a covariate in the depression severity ANCOVA models used in hypotheses 1a-2b above (as recommended by Miller and Chapman 2001).

4.4.3 **Test of Hypothesis 3c. Cerebral Blood flow.** *Lurasidone will increase striatal cerebral blood flow in all participants relative to placebo. Lurasidone's effects on reward and penalty processing in depression will not be confounded by baseline shifts in regional and global cerebral blood flow (CBF).*

In order to examine whether lurasidone increases resting CBF, a paired-sample t-test compared the whole-brain CBF maps collected after administration of lurasidone against those acquired after placebo in the whole sample (n=43). As shown in Figure 4.25, a paired-samples t-test across the whole-brain showed that lurasidone increased CBF in bilateral putamen. These results were very robust as increases in CBF in the putamen were significant at the peak level whole-brain analyses, FWE-corrected (left putamen $x = -26, y = -4, z = 2, t = 6.15: p = .002$, right putamen $x = 28, y = -2, z = 2, t = 5.50: p = .015$), which is a conservative threshold (Eklund et al., 2016a). Significant increases in blood flow were not observed in any frontal brain regions.

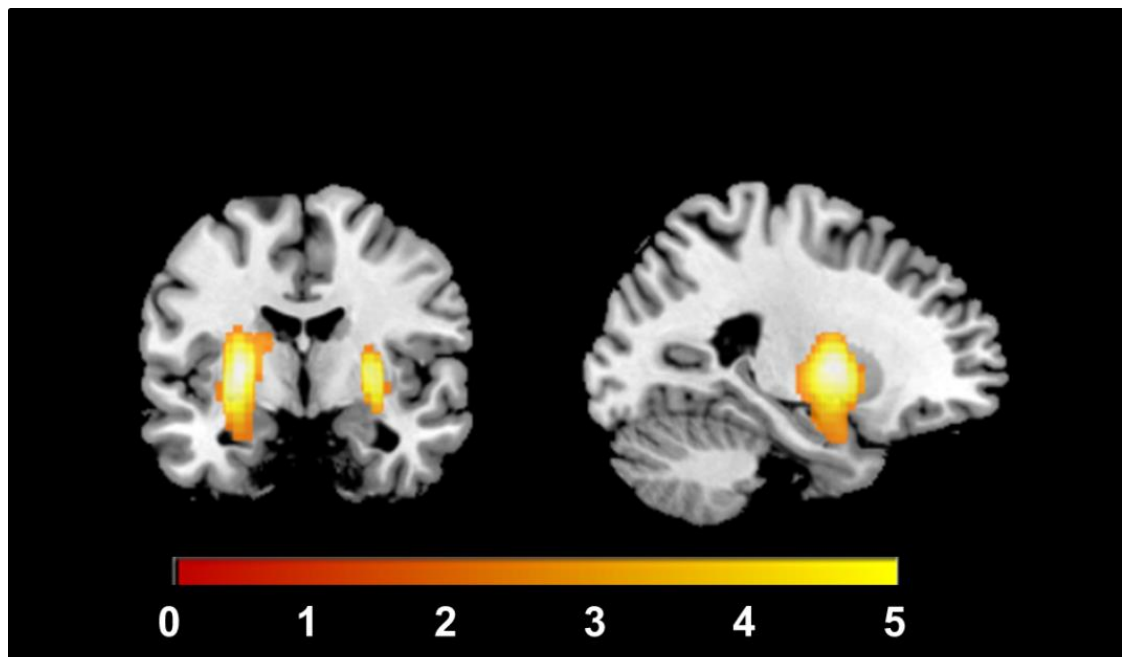


Figure 4.25. Increased cerebral blood flow in bilateral putamen for lurasidone relative to placebo during rest in the whole sample (n=43). Significant at the peak level whole-brain analyses, FWE-corrected (left putamen $x = -26, y = -4, z = 2, t = 6.15: p = .002$, right putamen $x = 28, y = -2, z = 2, t = 5.50: p = .015$). Bar represents T-value.

Average *global* mean CBF values (ml/100g/min) in grey matter for lurasidone were: 44.65 +/- 1.17; and for placebo were: 44.36 +/- 1.14; the average mean CBF values in the *putamen* under lurasidone were: 65.11 +/- 1.52; and under placebo were: 59.72 +/- 1.33; and the maximum CBF values in the putamen under lurasidone were: 75.82 +/- 1.67; and on placebo were: 70.01 +/- 1.62. These are displayed in Figure 4.26.

We next tested whether these global and striatal CBF values were related to depressive symptoms. Quantitative measures of mean global CBF and putamen CBF were extracted for each participant after placebo and lurasidone and entered into a repeated measures ANCOVA with the following factors: *Medication* (placebo, lurasidone) as the within-subject variable, *Medication Order* (placebo-lurasidone, lurasidone-placebo) as the between-subject factor, and *Depression Severity* (total BDI score) as the covariate of interest. The repeated measures ANCOVA revealed that the extracted global and striatal CBF values were not related to *Depression Severity* ($F=0.02$, $df=1$, 40 , $p=.903$), *Medication Order* ($F=0.44$, $df=1$, 40 , $p=.903$), or any three-way interactions with these respective factors ($F=0.01$, $df=1$, 40 , $p=.952$); ($F=1.10$, $df=1$, 40 , $p=.300$). Therefore, lurasidone increased striatal CBF regardless of depressive symptom severity, and this can be seen in Figure 4.26.

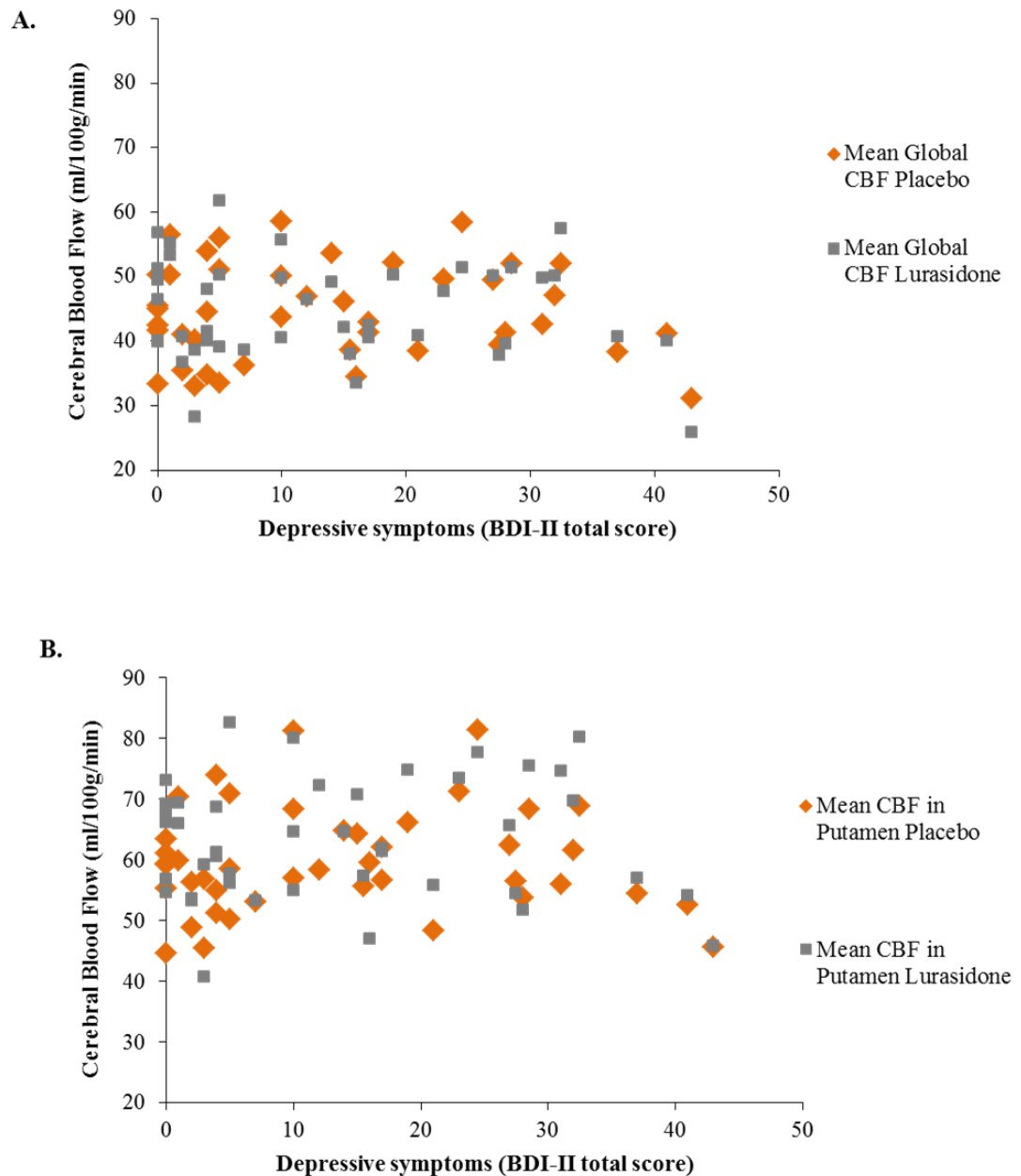


Figure 4.26. Mean (A) global and (B) regional (putamen) cerebral blood flow in grey matter across the entire sample ($n=43$) in relation to continuous depressive total symptom scores on the Beck's depression Inventory (BDI-II).

In order to ensure that the BOLD results in the ACC were independent of changes in underlying CBF, we tested the effects of acute lurasidone administration on global and regional blood flow. As shown in Figure 4.25 above, lurasidone increased CBF in bilateral putamen relative to placebo during rest in the whole sample ($n=43$) but

significant increases in blood flow were not observed in the ACC. The change in CBF values for each of the seven ROIs were extracted and used as covariates for the same region in the fMRI BOLD analyses. This did not lead to any changes in the results: non-significant results remained non-significant and significant results remained significant. In particular, the *Medication-by-Depression Severity-by-Outcome Type* interaction in the ACC ($F(1,36)=8.13, p=.007$) (Hypothesis 1d in Section 4.3.4 above). Moreover, we correlated the difference between BOLD responses to reward/penalty outcomes on placebo versus lurasidone with the change in global and regional CBF between the lurasidone and placebo visits. The rationale was that if BOLD signal changes were due to CBF changes, then the two changes should be correlated. We found that these global ($r=0.06, p=.749$) and regional putamen ($r=0.22, p=.199$) and ACC ($r=0.18, p=.306$) CBF values were not correlated with reward and penalty-related BOLD signal changes in the ACC. This suggested that the ‘main’ effect of lurasidone on CBF did not relate to the changes in signal on the task or the altered baseline was not behind the BOLD changes.

Chapter 5 - Discussion

This thesis examined three hypotheses for the effect of lurasidone on (1) neural correlates of reward and penalty processing and (2) reward and penalty-related prediction error signal and (3) cerebral blood flow (CBF) in depression.

Depression is characterised by hyporeactivity to reward (Admon et al., 2015a; Forbes et al., 2009; Forbes et al., 2010; Gotlib et al., 2010a; Knutson et al., 2008; Luking et al., 2016c; Olino et al., 2014; Pizzagalli et al., 2009b; Rzepa et al., 2017; Segarra et al., 2016; Sharp et al., 2014) and hyperactivity to penalties (Admon et al., 2015a; Engelmann et al., 2017; Gotlib et al., 2010b; Luking et al., 2016b), and thus an antidepressant effect could be brought about by increasing reward, decreasing salience to negative events, or, both simultaneously. Given the relative paucity of literature on processing of losses, this thesis was designed to interrogate both anticipation and feedback of rewards and penalties. Broadly speaking, we hypothesised a normalisation of fronto-striatal reward and penalty function and prediction error following acute-dose administration in depression. We anticipated that participants scoring high on depression would show a baseline difference in fronto-striatal activity which would be reverted by acute-dose lurasidone. Moreover, we sought to address a key concern in pharmacoinaging studies, namely that shifts in global or regional CBF could underlie changes observed in BOLD fMRI signal. We therefore also used ASL, an imaging modality that allows the quantification of cerebral blood flow at rest, to disentangle global and regional CBF changes from BOLD fMRI signal. As such, this was the first investigation examining the acute effects of lurasidone in the human brain (across a spectrum of depression severity), on a well-validated neuroimaging reward task, together with a concerted attempt to control for known potential confounds.

5.1 **Summary of results: effects of lurasidone on reward and penalty outcomes, prediction error and cerebral blood flow**

The results and how they relate to their respective hypotheses is summarised in Table 5.1. In this thesis, I compared the effects of lurasidone and placebo on neural responding to reward and penalties and CBF in medication-naïve young-adult subjects across the range of depression severity.

During the *anticipation phase* of the task we did not find evidence in favour of hypothesis 1a and 1b as there were no significant three-way interactions with depression severity and medication. Instead, we unexpectedly found a *Medication-by-Anticipation Cue* interaction such that lurasidone reduced responses to win and loss cues versus placebo, and potentiated responses for neutral cues in the ACC and caudate across the entire sample (i.e. regardless of depression and anhedonia severity).

In contrast, we found support for hypothesis 1d (lurasidone will reduce the penalty-related feedback signal. These effects will be most pronounced in individuals with higher depressive symptoms). Brain activity in the ACC to *Penalty Outcomes* in individuals with high symptoms of depression under lurasidone, but not placebo, resembled brain activity of individuals with low symptoms of depression. Specifically, lurasidone *reduced* ACC signalling to negative feedback in young people with elevated depressive symptoms. We found an opposite pattern of signal normalisation for *Reward Outcomes* in the ACC and NAcc. Lurasidone *enhanced* ACC and NAcc signalling to positive feedback in depressed individuals, however, this pattern did not remain significant after stringent correction for multiple ROI comparisons. Instead, we found that lurasidone significantly increased NAcc activation in individuals with higher symptoms of anhedonia as captured by the SHAPS anhedonia questionnaire. Thus, we found partial support for hypothesis 1c (lurasidone will increase the reward feedback signal in the caudate, putamen and NAcc. These effects will be most pronounced in individuals with higher depressive symptoms and consumatory anhedonia). We did not find any three-way interactions in the whole brain analyses (i.e. beyond the hypothesised regions). All the ROI results remained when the outliers were included in the analysis.

For the prediction error analyses, we found statistically significant support for an alteration in reward-related PE encoding (hypothesis 2a) in the amygdala and penalty-related PE encoding (hypothesis 2b) in the ACC in one of the three PE models, namely, the *Fixed PE model*. The other dynamic models did not show statistically significant alterations in PE encoding after Bonferroni correction for multiple ROI comparisons. The ‘normalisation’ effect in the Fixed PE model for penalty-related PE encoding in the ACC seemed to be a mirror of the results found for ACC activation to penalty outcomes.

We found evidence in favour of all three sensitivity analyses (hypotheses 3a, 3b, and 3c). First, there was no association between continuous anxiety severity measures and lurasidone’s effects on reward/penalty anticipation and outcome. Second, we found no evidence that an acute dose of lurasidone alters subjective ratings of state anxiety, overall sedation scores, nor its subcomponent factors of alertness and tranquillity. Third, we demonstrated that lurasidone significantly increased CBF in the striatum (namely the putamen) in all participants relative to placebo. Increased regional blood flow in the putamen under lurasidone, and changes in global blood flow did not drive the BOLD MID findings. Taken together, the sensitivity analyses confirmed that anxiety, self-reported changes in sedation and state anxiety, and baseline shifts in CBF did not confound lurasidone’s effects on reward and penalty processing in depression.

We also completed another set of analyses, which were not directly linked to our hypotheses, but nevertheless provided a foundation for validating the results of our hypotheses. In terms of behavioural performance on the MID task, we found good task adherence (high response rate and low number of premature responses) in all but one participant. We found that relative to placebo, lurasidone reduced the number of premature responses to penalty cues relative to neutral cues. However, there were no significant effects of medication on reward and penalty processing performance (total winnings, RTs and Accuracy). Instead, we found an effect of cue type on RT and accuracy such that there were faster and more accurate responses to reward and penalty cues relative to no-incentive cues. This suggests that the BOLD fMRI findings were not confounded by group differences in task performance. For the whole-brain analyses, we found that the MID task activated commonly reported regions of the brain during reward and penalty anticipation and outcome on placebo across the entire sample. We also showed that reward and penalty-related prediction errors were

encoded in the majority of our fronto-striatal-limbic ROIs. However, when validating the PE models we found that PE signalling could not be reliably distinguished from outcome magnitudes. Lastly, we showed that there were no significant effects of medication or depression severity on head movements in the scanner and no subjects were excluded due to movement differences.

Taken together, an acute dose of lurasidone normalises (reduces) neural ACC responses to negative outcomes and penalty-related PE, without modification of behaviour in individuals with elevated depressive symptoms. Lurasidone also normalises (increases) striatal (NAcc) responses to positive feedback as a function of increasing anhedonia severity. These results provide evidence for abnormalities in neural reward-penalty systems in depression and highlight the potential of targeted pharmacological treatments to normalise penalty and reward-related processing in depression and anhedonia respectively.

Table 5.1. Summary of the main hypotheses tested in this thesis with reference to the statistical models employed for testing the hypotheses, main results, and whether these hypotheses were supported.

Hypothesis	Test of hypothesis	Result from this study	Hypothesis supported?
Hypothesis 1a. Reward Anticipation. <i>Lurasidone will increase striatal activation during reward anticipation and these effects will be most pronounced in individuals with higher depressive symptoms and anhedonia.</i>	ROI: (caudate, putamen, NAcc, OFC, ACC, insula, amygdala) Omnibus model: Repeated-measures ANCOVA. Factors: <i>Medication</i> (placebo, lurasidone) and <i>Anticipation Cue</i> (neutral, win, loss) as within-subject variables, <i>Medication Order</i> as the between-subject factor, and <i>Depression Severity</i> (total BDI score) OR <i>Anhedonia Severity</i> (total SHAPS or DARS score) as the covariate of interest.	No significant interactions of anticipation cue with depression severity, anhedonia severity or medication. <i>Medication-by-Anticipation Cue</i> interaction such that lurasidone reduced responses to win and loss cues versus placebo, and increased responses for neutral cues in the ACC and caudate across the entire sample (i.e. regardless of depression and anhedonia severity).	No. Opposite direction.
Hypothesis 1b. Penalty Anticipation. <i>Lurasidone will alter the penalty-related anticipation signal in ACC, anterior insula, amygdala and striatal regions and these effects will be greatest in individuals with higher depressive symptoms.</i>	As above (but no test with anhedonia severity)	No significant interactions of anticipation cue with depression severity or medication.	No.
Hypothesis 1c. Reward Outcome. <i>Lurasidone will increase the reward</i>	Primary (continuous analyses) Omnibus model: Repeated measures ANCOVA	Primary (continuous analyses) Lurasidone had its strongest effect of increasing ACC	Partial support.

feedback signal in the ventral striatum, namely the caudate, putamen and NAcc. These effects will be most pronounced in individuals with higher depressive symptoms.

for each ROI. This included the factors: *Medication* (placebo, lurasidone) and *Outcome Type* (reward, penalty) as within-subject variables, *Medication Order* as the between-subject factor, and *Depression Severity* (total BDI-II score) as the covariate of interest.

Repeated measures ANCOVA for brain responses to *Reward Outcomes* with factors: *Medication* (placebo, lurasidone) as within-subject variables, *Medication Order* as the between-subject factor, and *Depression Severity* (total BDI-II score) or *Anhedonia Severity* (SHAPS or DARS total score) as the covariate of interest.

Secondary (categorical analyses)

Omnibus model: Repeated-measures ANOVA with *Medication* (placebo, lurasidone) and *Outcome Type* (*Reward Outcome* versus *Penalty Outcome*) as the within-subject variables and *Depression Group* (low (BDI-II score: 0-16) versus high (BDI-II score: 17-43) depressive symptoms) and *Medication Order* as the between-subject factors.

Repeated measures ANOVA for brain responses to *Reward Outcomes*

and NAcc responses to *Reward Outcomes* in individuals with high depression severity, however, this pattern did not remain significant after stringent correction for multiple ROI comparisons.

Lurasidone significantly increased NAcc activation in individuals with higher symptoms of anhedonia

Secondary (categorical analyses)

Medication-by-Depression Group-by-Reward Outcome interaction in the NAcc and ACC fell short of significance after Bonferroni correction.

Hypothesis 1d. Penalty Outcome. <i>Lurasidone will reduce the penalty-related feedback signal in the VS, ACC and insula. These effects will be most pronounced in individuals with higher depressive symptoms.</i>	<p><u>Primary (continuous analyses)</u></p> <p>Omnibus model: Repeated measures ANCOVA for each ROI. This included the factors: <i>Medication</i> (placebo, lurasidone) and <i>Outcome Type</i> (reward, penalty) as within-subject variables, <i>Medication Order</i> as the between-subject factor, and <i>Depression Severity</i> (total BDI-II score) as the covariate of interest.</p> <p>Repeated measures ANCOVA for brain responses to <i>Penalty Outcomes</i> with factors: <i>Medication</i> (placebo, lurasidone) as within-subject variables, <i>Medication Order</i> as the between-subject factor, and <i>Depression Severity</i> (total BDI-II score).</p>	<p><u>Primary (continuous analyses)</u></p> <p>Lurasidone had its strongest effect of decreasing ACC responses to <i>Penalty Outcomes</i> in individuals with high depression severity</p>	<p>Yes.</p>
	<p><u>Secondary (categorical analyses)</u></p> <p>Omnibus model: Repeated-measures ANOVA (as above).</p>	<p><u>Secondary (categorical analyses)</u></p> <p><i>Medication-by-Depression Group-by-Penalty Outcome</i> interaction was significant in the ACC. Post-hoc t-tests showed that brain activity to penalties in the ACC in individuals with elevated depression scores under lurasidone, but not placebo, resembles brain activity of healthy volunteers.</p>	
Hypothesis 2a. Reward-related Prediction Error. <i>Lurasidone will alter (increase or decrease) the reward-related PE signal in the striatum, OFC and ACC.</i>	<p>Omnibus model: repeated measures ANCOVA, where the within-subject variables included <i>Medication</i> (placebo, lurasidone) and <i>PE Type</i> (Reward PE, Penalty PE), the between-subject factor included <i>Medication Order</i> (placebo-lurasidone, lurasidone-placebo) and <i>Depression</i></p>	<p><i>Fixed PE model:</i> Under lurasidone, individuals with higher depressive symptoms had stronger reward PE encoding in the amygdala. However, this trend was not found under placebo.</p> <p>No significant results following Bonferroni</p>	<p>Yes for Fixed PE Model only.</p>

<i>These effects will be most pronounced in individuals with higher depressive symptoms.</i>	Severity (total BDI score) score was the covariate of interest. ANCOVA for reward and penalty PE separately for all three types of PE model: <i>Fixed PE model</i> , <i>Dynamic PE model for all cues combined</i> and the <i>Dynamic PE model for wins and penalty cues separately</i> .	correction for the <i>Dynamic PE model for all cues combined</i> and the <i>Dynamic PE model for wins and penalty cues separately</i> .	
Hypothesis 2b. Penalty-related Prediction Error. <i>Lurasidone will alter (increase or decrease) the penalty-related PE signal in frontal, striatal and limbic regions: VS, ACC, amygdala and insula. These effects will be most pronounced in individuals with higher depressive symptoms.</i>	As above.	<i>Fixed PE model:</i> Individuals with higher depressive symptoms under placebo had higher (more negative) encoding of penalty PEs in the ACC and this trend was not found under lurasidone. No significant results following Bonferroni correction for the <i>Dynamic PE model for all cues combined</i> and the <i>Dynamic PE model for wins and penalty cues separately</i> .	Yes for Fixed PE Model only.
Hypothesis 3a. <i>Lurasidone's effects on reward and penalty processing in depression will not be confounded by comorbid anxiety disorders.</i>	Tested for an association between dimensional anxiety scores and brain activation. If there were to be no association, then there would be no need to include it as a covariate in the depression severity ANCOVA models used in hypotheses 1a-2b above	No significant associations between brain activity and anxiety and no significant interactions between <i>Medication</i> , <i>Anxiety Severity</i> and <i>Anticipation cue/Outcome Type/PE</i> in any of the ROIs.	Yes.
Hypothesis 3b. <i>Lurasidone's effects on reward and penalty processing in depression will</i>	VAS and STAI-S change scores (pre-drug to peak-of-drug) entered into a repeated measures ANCOVA with <i>Medication</i> (placebo or lurasidone) as the within-subject variable,	No evidence that an acute dose of lurasidone alters subjective ratings of state anxiety, overall sedation scores, nor its subcomponent factors of alertness and tranquillity.	Yes.

5.2 Discussion of behavioural findings

Consistent with prior reports on adults with MDD, we did not find differences in behavioural performance as a function of depression severity thereby suggesting that the neural findings on group differences cannot be dismissed as artefacts related to a differing task performance (Admon et al., 2017). This is in line with findings from the literature review in Introduction Section 1.6 that the empirical association between brain and behaviour findings in reward processing in depression often do not overlap. Whereas many purely behavioural studies report a significant relationship between reward processing and depression (Henriques and Davidson, 2000; Henriques et al., 1994; Pizzagalli et al., 2008b; Vrieze et al., 2013b), very few neuroimaging studies demonstrate aberrations in depression that span the three levels of explanation: brain circuit, task behaviour, and clinical symptom (Keren et al., 2018, in press). This may be linked to the fact that many of the tasks used to study reward processing, notably the MID, are far from ideal for capturing behavioural effects (Lutz and Widmer, 2014). Developing tasks that can overcome such shortcomings will be important. Nevertheless, we did find that relative to placebo, lurasidone reduced the number of premature responses to penalty cues relative to neutral cues. This finding is in line with the neuroimaging results for penalty outcomes (discussed below) and fits with the idea of lurasidone making people less loss averse. However, this must be considered in light of the number of premature responses being quite low (floor effect).

Moreover, the absence of significant medication effects on reaction time may suggest that there were no sedative and thus motoric slowing effects of lurasidone. Indeed, this corresponds to the findings that lurasidone had no significant effects on subjective reports of mood, anxiety or sedation which could be explained by lurasidone's low affinity for histamine H_1 and muscarinic M_1 receptors (Ishibashi et al., 2010; Sanford and Dhillon, 2015). Another possibility is that the study did not have enough power to detect subjective or behavioural changes. However, as this study used similar scales and sample sizes to previous studies with acute pharmacological administration (see Literature Review Table 1.8 in Section 1.6), it could be that the reduced neural activity to penalties after lurasidone treatment does not necessarily become the subject of conscious awareness, although it could still presumably influence behaviour. In other

words, the neuropsychological effects of lurasidone could occur very early, whilst changes in behaviour may not be apparent with an acute dose. This would fit with other studies (Table 1.8), showing a lack of change in behavioural responses following, for example, acute administration of amisulpride in depressed and healthy volunteers (Admon et al., 2017). This could also potentially correspond to a cognitive neuropsychological model of antidepressant drug action, described in further detail in Section 5.6.1 below (Harmer et al., 2009b). However, whether lurasidone might affect these processes in studies with larger sample sizes of MDD patients and over a longer period of time remains to be elucidated.

5.3 Anticipation results discussion

Our results of attenuated responses in the ACC and caudate across cue valences can be likened to the effects of SSRI agents and dopamine antagonist olanzapine (Abler et al., 2007). Acute dose and seven-day treatment with SSRI paroxetine diminished brain activity induced by motivation in healthy subjects in the globus pallidus, insula, putamen, ACC and dorsolateral prefrontal cortex (Abler et al., 2012; Abler et al., 2011; Marutani et al., 2011). Treatment with the SSRI citalopram in healthy controls reduced activation for rewarding and aversive stimuli (in the VS and ventromedial OFC to rewarding stimuli (chocolate) and in the lateral OFC for aversive stimuli) (McCabe et al., 2010). Thus, lurasidone, like SSRIs may induce a general dampening of the salience of reward and penalty cues.

It may seem paradoxical that lurasidone reduced neural responses during reward anticipation, since depression, and in particular-anhedonia, is related to blunted responses during reward anticipation (Arrondo et al., 2015; Hagele et al., 2015; Luking et al., 2016c; Olino et al., 2014; Smoski et al., 2009; Stoy et al., 2012a). In this context, we may expect that drugs with known antidepressant properties normalise responses by potentiating striatal activity to reward anticipation. Indeed, this was the basis for hypothesis 1a, and is coherent with findings of potentiated striatal responses with acute (low dose) amisulpride (Admon et al., 2017). However, opposite responses (and in line with our findings) (Hawkins et al., 2018, in press) have also been found with higher doses of dopamine antagonists (Jocham et al., 2014). Thus, an affinity-based model (discussed in Section 1.6.3.4), could be applied here to understand the

observed association between low dose D₂ antagonist and higher reward coding and between high dose and attenuated reward coding. Specifically, presynaptic D₂ receptors have higher affinity to dopamine than post-synaptic D₂ receptors and would be occupied first at low doses (Frank and O'Reilly, 2006a). Predominant blockade of presynaptic autoreceptors at low doses could subsequently lead to amplification of dopamine phasic release (also described as a shift of the tonic versus phasic balance towards phasic activity (Dreyer et al., 2010). There is a clear need for studies using varying doses of dopamine antagonists on phasic versus tonic dopamine firing and release to understand the pre-synaptic actions of dopamine antagonists. I provide further explanation of how synaptic mechanisms may explain this blunting of anticipatory signals in Section 5.6.2 below.

Another possibility is that anticipatory blunting reflects a temporal issue. Antidepressants seem to exacerbate reward deficits early in treatment (Kumar et al., 2008; Marutani et al., 2011; McCabe et al., 2010) prior to normalisation following longer-term (two-six week) treatment (Scholl et al., 2017; Stoy et al., 2012a; Walsh et al., 2017). Again, further testing would be required to fit this explanation to lurasidone (i.e. increasing anticipation of rewards with more chronic exposure to the drug). Although speculative, it could be the case that the findings fit a behavioural activation model of the antidepressant mechanism of action of lurasidone in which consummatory pleasure must first be experienced, and with time, anticipation increases for rewarding events.

5.4 Discussion of findings from the outcome phase

5.4.1 Reward Outcome

5.4.1.1 *Reduced reward-related NAcc activity and depressive symptoms on placebo*

Before turning to a discussion of hypotheses 1c (i.e. the association between neural correlates of reward outcomes, medication and depression/anhedonia), it is useful to comment on the results seen on placebo alone. We found that NAcc activity to reward outcomes was negatively correlated with depression and anhedonia severity on

placebo. Thus, our findings are in line with prior research that implicates blunted NAcc responses to positive experiences with increasing depression severity and anhedonia both for instrumental tasks (Pizzagalli et al., 2009b; Steele et al., 2007) and passive tasks (McCabe et al., 2009). As this association has previously been found using passive tasks (i.e. experience of primary rewards with no learning stimulus-response component), it provides support for the notion that neural activity during the outcome phase could reflect direct responses to the outcome (experience of pleasure or value). However, the dominant model of striatal dopamine activity is that the salience or anticipatory activity predicts the outcome in cued-reward tasks (Schultz et al., 1997). In this context, any blunting in anticipatory processing or reduction in salience of cues (associated with depressive illness), could also affect outcome processing. Accordingly, blunted striatal activation to reward outcomes could indicate weaker perceived action-outcome relationship and/or weaker responses to unpredictable rewards in depression.

5.4.1.2 ***Association between reward-related NAcc activity, medication and depression/anhedonia***

With respect to the hypothesis 1c, we found a significant increase in NAcc signalling to positive feedback with increasing anhedonia but not depression severity, after stringent correction for multiple ROI comparisons. Importantly, this significant result was found only with the SHAPS questionnaire, and not the DARS anhedonia questionnaire. The SHAPS is concerned with consummatory anhedonia, and factor analysis of the SHAPS in other studies has demonstrated that it primarily loads onto hedonic capacity (Leventhal et al., 2006; Nakonezny et al., 2010; Nakonezny et al., 2015). In contrast, the DARS total score which was used in the analyses pooled anticipatory and consummatory anhedonia scores. Thus, it may be that the SHAPS scores better map onto this stage of reward processing. The lack of a significant normalisation result using broader anhedonia definitions and depression severity (BDI-II) (which includes other symptoms such as low mood and sleep problems) may suggest a ‘dilution’ in specificity and power to detect an effect. Moreover, our result may support a growing evidence for the conceptualisation of anhedonia as a dual construct: motivational anhedonia (deficit in motivation and effort expenditure) and consummatory anhedonia (deficit in pleasure experience), with the results of our study

concerning the latter (Treadway, 2016; Treadway et al., 2012; Treadway and Zald, 2011).

This leads on to the next question which concerns what an increase in striatal activity to reward outcomes could actually represent: is lurasidone boosting pleasure *experience* or reward-related *encoding* in individuals with elevated anhedonia? As reviewed in the introduction (Section 1.4 and 1.5), the outcome phase is a complex period in which multiple processes occur simultaneously. These include the response to the outcome itself (including information about its pleurability or value), evaluation against expectation (i.e. a PE), integration into memory and preparation for the next trial.

Anhedonia has previously been associated with reduced hedonic capacity and diminished reward learning in probabilistic reward tasks relative to those with low anhedonic symptoms (Pizzagalli et al., 2008c; Vrieze et al., 2013b). Therefore, at a conceptual level it is plausible that lurasidone could be affecting both processes in individuals with elevated anhedonic symptoms. The differential effect of lurasidone on reward anticipation (attenuation) and outcome (potentiation) calls to mind the Schultzian PE model of dopaminergic activity (Schultz, 1998; Schultz, 2016; Schultz et al., 1997). An interpretation in line with this model would be that lurasidone reduces anticipatory encoding which would subsequently lead to increased reactivity to outcomes. However, there were unexpectedly no significant results for reward-related PE in the NAcc and in fact, none of the ROIs showed an association between reward-related PE activation and increasing depression/anhedonia severity. Thus, an increase in NAcc activity to reward outcomes by lurasidone could reflect a potentiation of subjective pleasure experience or value in individuals with higher anhedonia scores. This would be predicted to be associated with increased opioid receptor activity, but dopamine is known to have an excitatory effect on opioid-induced reward (Cook et al., 1999). How lurasidone, a dopamine antagonist would affect opioid-mediated experiential processes during the feedback phase is not known (Berridge and Kringelbach, 2015; Berridge et al., 2009; Di Chiara and North, 1992).

5.4.2 **Penalty Outcomes**

5.4.2.1 ***Elevated penalty-related ACC activity and depressive symptoms on placebo***

Participants with higher depression severity on placebo showed greater ACC response to negative feedback. This is congruent with evidence of heightened sensitivity to negative outcomes in depression and its association to elevated loss-related signals in the ACC, and connected regions such as the anterior insula and striatum (Admon et al, 2015; Engelmann et al, 2017; Gotlib et al, 2010a; Luking et al, 2016a; Quevedo et al, 2017). Indeed, Admon et al., (2015) showed increased caudate-ACC connectivity during penalties and suggested that this could represent a neural mechanism for the abnormally increased representation of negative feedback upon the completion of an (unsuccessful) action in MDD (Admon et al., 2015a). In particular, it has been postulated that increased ACC activity in depressed individuals to loss outcomes reflects biased stimuli representations that mediate choice behaviour, including preferential attention, planning and self-referential processing towards losses (Gotlib et al, 2010a; Grimm et al, 2009; Sylvester et al, 2003).

5.4.2.2 ***Association between penalty-related ACC activity, medication and depression/anhedonia***

Our findings are consistent with the notion that acute dose anti-depressants can have an effect on brain processes implicated in depression (Harmer et al., 2017). The effects of penalty-related signal normalisation by lurasidone were localised to the ACC, a region that integrates diverse striatal and prefrontal functions (Haber and Knutson, 2010). For example, the ACC and ventral striatum (VS) show functional connectivity at rest (Pan et al, 2017) and input from the ACC to the VS allows for flexible deployment and adaptation of behaviour to changing circumstances (Alexander and Brown, 2011; Holroyd and Coles, 2002; Holroyd and Umemoto, 2016; Holroyd and Yeung, 2012; Shahnazian and Holroyd, 2017; Umemoto and Holroyd, 2016; Walsh and Anderson, 2012; Walton et al, 2007). Electrophysiological (EEG) studies have shown that the Feedback Negativity (FRN), an event-related potential which indicates the early appraisal of feedback and appears larger following the presentation of negative feedback, has its origins in the ACC (Gehring and Willoughby, 2002; Hajcak et al, 2005; Holroyd et al, 2002; Holroyd et al, 2004; Yeung et al, 2005). Specifically,

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an FRN signal may be generated as ACC neurons shift from encoding expected to actual outcomes (i.e. a PE signal) (Hyman et al, 2017). This raises a similar question to the one discussed in the reward outcomes section above: is lurasidone attenuating the *experiences* associated with negative feedback (e.g. disappointment, self-referential processing towards losses) or reducing *penalty-related (expectation-outcome) encoding* in individuals with elevated depressive symptoms? For this, it is useful to refer to the prediction error findings in Section 5.4.3 below.

With reference to other acute pharmacological intervention studies, neural blunting of aversive responses parallels studies using SSRIs (McCabe et al., 2010). Indeed, SSRI treatment is associated with an experience of emotional constraint in which the emotional responses to both pleasurable and aversive experiences are diminished, or the salience of both rewarding and aversive stimuli is lost (Opbroek et al., 2002; Price et al., 2009; Zald and Depue, 2001). This has shown to be associated with experimental studies in animals and humans indicating that serotonin pathways exert an inhibitory influence over neural systems mediating positive and negative affective processes (Zald and Depue, 2001). Thus, SSRIs may be clinically useful in disorders characterised by painful and disabling negative affect (Arroll et al., 2009; Nutt et al., 2007); but this needs to be balanced against their inhibitory effects on the neural responses to reward. This stands in contrast to the findings in our study in which there was not a ‘general constraint’ of emotional responses, as there was also a (non-significant) trend for increased responses to reward outcomes with lurasidone in individuals with high depressive symptoms. The non-significant trend in our study may reflect low power rather than a spurious finding (this explanation is strengthened by the fact that this trend was found in several other brain regions too) and a significant relationship was found with anhedonia severity. Indeed, if this result were to be found in larger sample, one could argue that lurasidone has an optimal profile by increasing responses to rewards and reducing response to negative outcomes.

5.4.3 **Reward and penalty-related PE results**

Hypothesis 2a was supported by the finding that individuals with higher depressive symptoms under placebo had higher (more negative) encoding of penalty PEs in the ACC and this trend was not found under lurasidone. This ‘normalisation’ effect seems

to be a mirror of the results found for ACC activation to penalty outcomes (hypothesis 1d). At first glance, this would suggest that lurasidone's effects on penalty outcomes can be understood in the context of medication-induced reduction of *penalty-related (expectation-outcome) encoding* in individuals with elevated depressive symptoms. However, the analyses we did to examine whether PE signalling could be reliably distinguished from outcome magnitudes suggest that this conclusion is not justified. The high correlations between the PE and feedback outcomes precluded a meaningful decomposition of the PE signal into its underlying constituents (as has been suggested previously, Chowdhury et al., (2013)). Thus, while the goal of the PE analyses was to investigate acute modulation of PE signaling in MDD by lurasidone, it should be noted that with respect to reward and penalty processing, the results of the group analyses cannot be unambiguously related to neural coding of PEs. Instead, the results may partly reflect the neural processing of reward and penalty outcomes and this means that the results of the *Fixed PE model* need to be interpreted with caution. Indeed, it is also worth reiterating that the MID task design itself is not a learning task as the contingencies were known prior to the data collection from the training. However, other notable approaches to studying PE, (e.g. Rutledge et al., 2014; 2017), also don't employ a learning task. In this context, the probabilities lead to uncertainty and the PE effects could relate to uncertainty. For this reason, we also cannot be sure that lurasidone affected the learning signal. The fixed PE model suggests that the learning signal may well be affected in a different task design that emphasised the learning of the contingencies, but here it is not possible to clearly separate learning from the probabilistic contingencies. The two *Dynamic PE models* certainly help here to emphasise the conclusion about learning over probabilistic contingencies, however no significant findings were found with these models. Nevertheless, the direction and size of the effect was similar across models.

Future analyses could use a more thorough framework (such as that used by Rothkirch et al., (2017)) in order to distinguish the neural coding of PEs from the neural responses to outcome magnitude with certainty. In line with Behrens et al., (2008) and Chowdhury et al., (2013), the neural PE signal should be accompanied by the neural signature of the two PE constituents: actual and expected outcome (the difference between these two components forms the PE). According to this framework, neural responses at the onset of the monetary outcome phase should have a positive

correlation with the actual outcome and a negative correlation with the expected outcome for reward-related PEs (and vice versa for penalty-related PEs). Using this approach, Rothkirch et al., showed that expected values and actual outcome magnitudes had differential relationships between anhedonia levels and neural responses in the VS and mOFC (Rothkirch et al., 2017). Specifically, actual outcome correlated negatively with anhedonia severity in the VS and mOFC, whereas expected value demonstrated no correlation with the VS and a positive correlation with OFC neural responses. Thus, the latter findings show that a change in computing the difference between expected and actual outcome (i.e. PE), had a role in anhedonia severity. Although this study could not differentiate PE responses in the VS and mOFC from responses to outcome magnitude, they showed a differential relationship between neural responses to expected and actual outcomes in the mOFC and anhedonia severity. This result would have not been found using a simple contrast of reward versus neutral outcomes.

It is also important to mention the changes in reward PE in the amygdala. The amygdala has dopamine innervations and receives a dense projection from the striatum (Haber and Knutson, 2010), and has previously shown to be sensitive to DA modulation during reward processing in healthy volunteers (Murray, 2007a; O'Daly et al., 2014; Russo and Nestler, 2013; Tye et al., 2010a). An unexpected finding was that on lurasidone, individuals with higher depressive symptoms had stronger reward PE encoding in the amygdala, with this trend not being found under placebo. This result is unique to all the other trends in the thesis because there were no baseline differences in reward-related PE encoding between individuals low and high on depressive symptoms on placebo, and thus no possibility for a 'normalisation' effect by lurasidone. Instead, it seems that lurasidone had opposite effects on reward PE encoding in low (reward PE attenuation) versus high (reward PE potentiation) depression severity participants. Perhaps inter-individual baseline differences in dopamine receptor availability and binding potential between low and high depression severity subjects could account for differential effects following a pharmacological challenge but not on placebo (Sheline et al., 2004; Suhara et al., 1992; Yatham et al., 2005; Yatham et al., 1999). This is described in more detail in Section 5.6.2 below.

5.5 Association with continuous anxiety severity

This thesis also addressed the potentially confounding effect of comorbidity which has not received much attention in previous studies. This is an important consideration given that it is firmly established that depression often co-occurs with other internalising symptoms (i.e. heterotypic comorbidity) (Caron and Rutter, 1991; Angold et al., 1999) and lurasidone has anxiolytic as well as antidepressant properties (Ishibashi et al., 2010). In line with the sensitivity analyses (hypothesis 3a), we found no association between continuous anxiety severity measures and lurasidone's effects on reward/penalty anticipation and outcome. In the context of our results, this suggests that the impact of lurasidone on reward and penalty outcome in individuals with elevated depressive symptoms is robust.

Our findings differ to the few studies which have examined co-occurring anxiety symptoms in depressed samples. For example, anxiety symptoms have been associated with higher activation in orbital frontal and ventral striatal regions during reward processing (Bar-Haim, et al., 2009; Forbes et al., 2006; Guyer et al., 2006), albeit not with the MID reward paradigm. Other studies have shown that co-varying for anxiety symptoms does not impact upon brain activity-depression associations and that activation patterns do not differ for MDD adults with (N=14) or without (N=16) comorbid anxiety (Forbes et al., 2009; Pizzagalli et al., 2009). There is still insufficient evidence for how anxiety relates to changes in frontal regions during penalty processing, and in the context of pharmacological challenges. Thus, with respect to anxiety symptoms, this study only provides preliminary evidence and needs further replication in future studies of reward and penalty processing in depressed or at risk samples.

5.6 Potential antidepressant mechanism of action of lurasidone

5.6.1 Neuropsychological level of explanation

In an attempt to explain lurasidone's potential mechanism of action, we can refer to different levels of explanation: system or synaptic level and I will begin with the former. A potential mechanism of beneficial antidepressant drug action of lurasidone could consist of reducing neural activation to feedback of negative events. This initial change may lead to a cascade of processes ultimately leading to improved mood. However, it must be noted that this proposal is highly speculative and further research, e.g. alleviation of depression through lurasidone intervention targeting the ACC, is required for establishing its role as a causal event.

In the context of the *neuropsychological model of antidepressant action* (Harmer et al., 2009a), it could be that lurasidone promotes reduced reactivity and biases to negative events and may therefore lead to changes in how stressors, life events and interpersonal interactions are managed and remembered. In line with a *behavioural activation model* (Dimidjian et al., 2011; Lewinsohn and Amenson, 1978), these early neurocognitive changes may promote reduced aversive-avoidant behaviours in patients with depression and greater reinforcement for healthy behaviour. In line with a *learned helplessness model*, a reduction in 'catastrophic responses' to perceived failure (Elliott et al., 1997a; Elliott et al., 1996) could reinstall a perceived sense of control and prevent a cycle of learned helplessness. Over time, the cumulative effect of neuropsychological and behavioural changes may culminate in improved mood.

In addition to an effect on negative feedback, and in line with the discussion in Section 5.4.2.2, lurasidone may increase experiences of reward, but only in individuals with elevated anhedonia symptoms. In line with a behavioural activation model, increased hedonic capacity could reinstall motivation to engage in positive activities. Testing of this hypothesis would require a longitudinal neuroimaging study of lurasidone.

In sum, the translation of rapid change in penalty processing by lurasidone into improved mood and conscious appraisal, may involve time, exposure to a real-world

environment and re-learning stimulus-response associations in the context of reduced processing biases and PEs to negative events and enhanced experiences of pleasure.

With these findings in mind it would be interesting to complete a study as in Wichers et al., (2009). Through experience sampling methods, they showed that it was antidepressant-induced increases in rewarding experiences, and not reductions in penalty or stress-sensitivity that distinguished responders to non-responders to treatment (TCA imipramine). Thus, it may be positive emotions, such as contentment, happiness, that offer resilience. In line with this, sustained activation in the ACC during *reward outcomes* predicted response to psychotherapy; patients with greater sustained activation in this region were more responsive to BA treatment (Carl et al., 2016b). However, whilst Carl et al., used a MID task with ‘missed win outcomes’, they did not include penalty outcome, and therefore, it cannot be ruled out that responses to penalties may also be important for predicting response to treatment.

5.6.2 **Synaptic mechanism of action**

In the previous section I have discussed lurasidone’s effects at the neuropsychological level. In this section I attempt to link these effects to potential changes in neurotransmitter systems at the receptor level (i.e. how actions at the receptor may explain the observed pattern of neuropsychological effects). Indeed, the main putative change affected by SGAs is through modulation of neurotransmitter actions, with dopamine being a major focus in reward and penalty processing, depression and its treatment. Although it must be noted that ascribing the changes seen to one or more receptor systems is highly speculative as the precise mechanism by which BOLD signal is modulated cannot be determined with fMRI alone (see Box 5.1).

Nevertheless, the next section attempts to consider potential mechanisms of action which could lead to two key results of this study, namely: *(i) Why/how could lurasidone reduce striatal and ACC activation to anticipation of both wins and losses? (ii) Why/how could lurasidone decrease responses to loss outcomes?*

The mechanisms described below are based on an underlying assumption that changes in dopaminergic function are reflected in the related BOLD signal. In favour of this, there is evidence for the role of dopamine in the motivational salience of environmental stimuli whether positively or negatively valenced (Matsumoto and Hikosaka 2009). For example, Knutson et al., (2004) found that amphetamine administration modulated prefrontal and striatal activations produced by monetary reward and loss. Moreover, an increase in DA release is spatially and temporally correlated to an increase in BOLD signal in the context of reward processing (Knutson and Gibbs, 2007; Schott et al., 2008b). Recently, a direct link has been found between reduced mid-brain transporter density and neural activity during reward processing within the mesolimbic pathway in healthy and depressed human participants (Dubol et al., 2017b). This evidence supports an association between dopamine release and BOLD signal. With fMRI, it is not possible to quantify lurasidone's relative action at each receptor type. In order to extrapolate their relative contribution, an appropriate approach would be to investigate the effects of drugs with highly selective receptor profiles on reward and penalty processing. However, highly selective drugs generally do not show clinical efficacy in depression, and thus it may be the interaction of various different neurotransmitter systems that is the critical feature for antidepressant effects (Brugue and Vieta, 2007). A fruitful approach would be to do head-to-head comparisons of incremental dosages of lurasidone and other dopamine antagonists with antidepressant properties (e.g. quetiapine) in combination with other imaging modalities (PET, MR spectroscopy and EEG).

Box 5.1. Dopaminergic neurons and the BOLD signal.

5.6.2.1 **Potential Mechanisms**

Mechanism 1: Lurasidone's D₂ antagonism reduces dopamine availability

According to this mechanism, lurasidone's antagonism at D₂ receptors could act to block and reduce dopamine release, thereby also attenuating the BOLD signal. This mechanism would support our result of reduced BOLD signal to the anticipation of win and loss cues in the ACC and caudate, as well as penalty outcomes in the ACC.

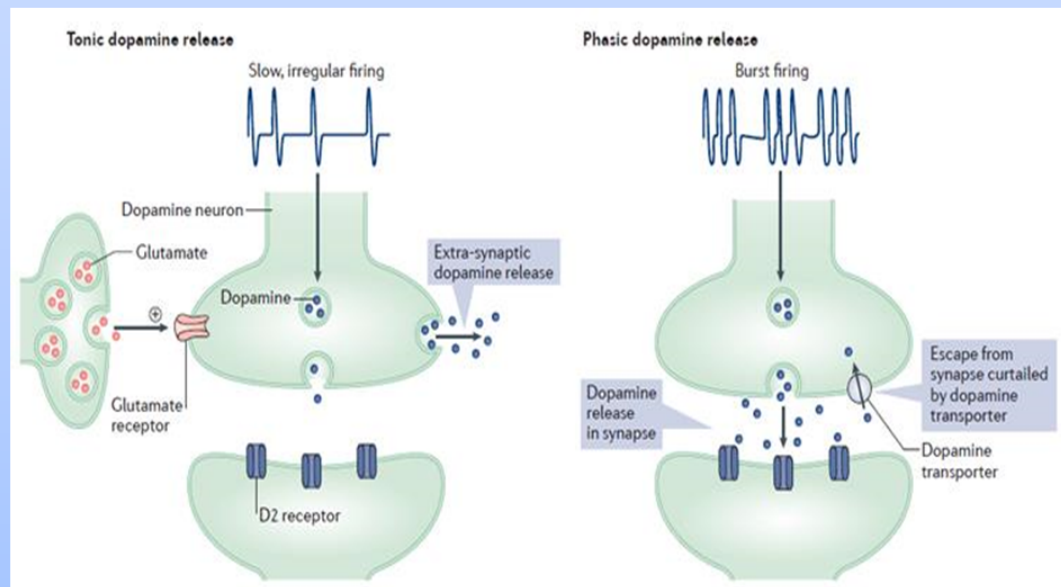
In favour of this, haloperidol, (a typical antipsychotic and a prototypical D₂ antagonist) reduces reward-related striatal activation during anticipation and decision-making (Oei et al., 2012b; Pessiglione et al., 2006; Pleger et al., 2009b). However, lurasidone has a loose D₂ postsynaptic occupancy and thus a faster dissociation time than FGA haloperidol, and to this end, it may be more appropriate to compare it to other SGAs. Indeed, atypical antipsychotics with lower and less prolonged occupancy of D₂ receptors and broader receptor binding profiles (e.g. olanzapine and amisulpride), do not consistently reduce neural responses during reward anticipation (Abler et al., 2007), and in fact have shown to potentiate anticipatory responses (Admon et al., 2017). This leads me on to the second potential mechanism.

Mechanism 2: Lurasidone increases dopamine availability via presynaptic autoreceptor blockade

Lurasidone may, at low doses, like amisulpride increase striatal dopamine release by preferentially blocking presynaptic dopamine autoreceptors. This could lead to one of two potential effects on BOLD signal. First, increased availability of dopamine, and increased firing of dopaminergic neurons could potentiate BOLD responses during anticipation and outcome, as has been found previously with amisulpride (Admon et al., 2017). Second, lurasidone may increase presynaptic dopamine availability, which may act to increase tonic levels of dopamine. This could in turn decrease the phasic firing of dopamine neurons and the sensitivity of the dopamine reward system (Grace 1991), thereby potentially reducing BOLD signal. For example, Knutson et al., (2004) modelled this in healthy volunteers. They showed that administering amphetamine caused large releases of striatal dopamine, and subsequently reduced BOLD response to reward anticipating cues. As our findings showed *reduced* ACC BOLD signal to *penalty outcomes* in addition to both anticipation of win and loss cues, the second explanation is most fitting. This is important given that these previous studies did not explicitly consider the outcome phase. An extensive number of studies by Grace (1991, 2016) provide a detailed explanation of the regulation of midbrain dopamine neurons and the relationship of phasic and tonic dopamine neuron firing is described in further detail in Box 5.2.

It must be emphasised that these are subcortical models that I am applying to the cortical (ACC) results in our study. These models are based on neuronal recordings which project to the ACC and microdialysis, usually in the striatum, but as yet, no study has measured both simultaneously and no study has included the ACC. This has clear limitations as there are regional (frontal versus striatal) differences in dopamine receptor distribution and signaling pathways. These subcortical-cortical differences are likely to lead to differential effects of the same pharmacological agent at these regions (Hernaus and Mehta, 2016). Therefore, this thesis emphasises the importance of expanding the existing research into cortical release, particularly in depression models. Nevertheless, the ACC is a region showing the highest cortical DA innervation in humans, which is an important consideration for the results of this thesis (Camus et al., 1986; Tassin et al., 1978).

Alterations in the firing of dopaminergic neurons mediate the characteristics of dopamine release (see figure below). Baseline tonic firing is related with tonic, extra-synaptic dopamine levels and occurs in a slow and irregular pattern (Floresco *et al*, 2003; Grace, 1991; Grace, 2016). In contrast, phasic dopamine neuron firing is related to rapid, high-amplitude, intra-synaptic phasic release (Floresco *et al*, 2003). Under normal circumstances, approximately half of the dopamine midbrain neurons are inhibited by GABAergic inputs from the ventral pallidum, and only uninhibited neurons fire tonically in a slow and irregular pattern (Grace, 1991). Tonic discharge effectively determines the functional output of dopamine neurons because it sets the level of responsivity of the system to phasic firing. In other words, only the uninhibited tonically firing population are free to switch to rapid phasic firing in response to a rewarding stimulus. Depending on the context (e.g. threatening versus non-threatening), the VP adapts by allowing more or less dopamine neurons to be active and this allows the system to become more or less responsive (Grace, 2016). When tonic dopamine neuron firing increases (i.e. more neurons are firing), the amplitude of the phasic response also increases. However, tonic dopamine release does not always correlate with phasic response amplitude. For example, if tonic dopamine release increases independently of population activity (e.g. via pharmacological presynaptic dopamine release, diminished re-uptake), the result is an attenuation of phasic dopamine release via dopamine auto-receptor inhibition. In this context, increases in tonic extracellular dopamine dampen the transient release phasic burst firing. This provides a context in which the phasic signals that mark rewarding stimuli are 'drowned' out and do not appreciably change the BOLD signal. The implication is that dopaminergic-pharmacological agents could act in a context-dependent manner such that they interact with differences in baseline tonic firing, dopamine sensitisation and/or extracellular levels of dopamine to affect BOLD signal.



Box 5.2. Tonic and phasic dopamine neuron firing and dopamine release. Figure taken from Grace et al., (2016) with permission.

Mechanism 3: Lurasidone's effects on serotonergic receptors modulates dopamine availability

Lurasidone, like other D₂ antagonists with antidepressant efficacy, such as quetiapine, have antagonistic activity at 5-HT_{2A} and 5-HT₇ receptors and partial agonist activity at serotonin 5-HT_{1A} (Horisawa et al., 2013; Ishibashi et al., 2010). Indeed, cortical regions which form part of the incentive-based learning network, such as the OFC and ACC have high densities of 5-HT (1A and 2A) receptors (Boureau and Dayan, 2011; Macoveanu, 2014). This is of particular interest as our findings were localised to the ACC. Ascending serotonergic systems show a similar innervation pattern to dopamine and in addition to the overlapping anatomical organisation of these neurotransmitter systems, there is evidence of their interaction at a functional level (Boureau and Dayan, 2011; Briand et al., 2007). This is illustrated in Table 5.2 and the relationship between dopamine and serotonin collectively gives rise to a mix of competitive, cooperative interactive associations between processing of reward and punishment.

Before explaining mechanism 3, it is important to describe how serotonergic systems can impact upon and regulate dopamine availability (Esposito et al, 2008; Azmitia and Segal, 1978; Beart and McDonald, 1982; Herve et al, 1987; Parent, 1981; Geyer et al, 1976; Egerton et al, 2008; De Deurwaerdere et al, 2004; Higgins and Fletcher, 2003; Lavoie and Parent, 1990; Spoont, 1992; Harrison et al, 1997; Nedergaard et al, 1988). There are at least fourteen different receptor subtypes for 5-HT (Cooper et al., 2002). Whilst 5-HT_{2C} receptors generally tonically inhibit DA release, the majority of 5-HT receptor types (5-HT_{1A}, 5-HT_{2A}, 5-HT₃, 5-HT₄) increase dopamine release in the NAcc via excitatory influence on the VTA. Indeed, 5-HT_{2A} receptors are present on presynaptic dopamine neurons, and blockade of these receptors increases dopamine release (Yatham et al., 2005). Lurasidone, like other AAPs blocks 5-HT_{2A} receptors and this is expected to increase dopamine levels (particularly in the cortex), as has been found previously with olanzapine and quetiapine (Ichikawa et al., 2002; Koch et al., 2004). Animal studies have also shown that AAPs increase dopamine release by stimulating 5-HT_{1A} receptors in the prefrontal cortex (Ichikawa et al., 2002). The role of 5-HT in increasing dopamine release has been shown experimentally with lurasidone. Specifically, Huang et al., (2012) tested whether lurasidone's 5-HT_{1A} partial agonism and/or 5-HT₇ antagonism, contributed to the ability of lurasidone to enhance dopamine release. They showed that lurasidone, like other atypical

antipsychotics, produced a dose-dependent increase in DA efflux in the prefrontal cortex, hippocampus and NAcc of rats. In addition, a 5-HT_{1A} receptor antagonist partially blocked the lurasidone-induced dopamine efflux, whereas a 5-HT_{1A} agonist and a 5-HT₇ receptor antagonist potentiated the effect of lurasidone to increase DA efflux, especially in the prefrontal cortex. These findings suggest that 5-HT_{1A} receptor agonism and affinity to 5-HT₇ is involved in the effect of lurasidone on dopamine efflux.

The exact mechanisms by which serotonin regulates dopamine release appears diverse and mirrors the complexity of DA regulation itself (Table 5.2). For instance, this process could involve changing the bursting behaviour of dopaminergic neurons (Di Giovanni et al, 1999), altering the relative balance between regional DA concentrations (De Deurwaerdere and Spampinato, 1999), or modulating the projections that control DA release (Bortolozzi et al, 2005). Moreover, regulation could be conditional on DA being activated, or could be tonic (Leggio et al, 2009b; Lucas et al, 2001; Porras et al, 2003; De Deurwaerdere et al, 2005).

Again, as detailed in mechanism 2 and Box 5.2, an increase in dopamine availability (but this time via action at serotonergic receptors primarily in the cortex) could lead to one of two potential effects on BOLD signal. First, increased availability of dopamine, and increased firing of dopaminergic neurons could potentiate BOLD responses during anticipation and outcome, as has been found previously with amisulpride (Admon et al., 2017). Second, lurasidone-induced increases in dopamine availability could in turn decrease the phasic firing of dopamine neurons and the sensitivity of the dopamine reward system (Grace 1991), thereby reducing BOLD signal. The latter is a better fit to our findings which showed reduced BOLD signal to both anticipation of win and loss cues, and penalty outcome.

Table 5.2. Aspects of serotonin function which indicate competition, collaboration or neither. Adapted from Boureau et al., (2011).

Relationship between dopamine (DA) and serotonin 5-HT	Observation
Opposing	<ul style="list-style-type: none"> -Tonic inhibition of accumbal DA release by 5-HT (Hervé <i>et al</i>, 1979, 1981) -5-HT_{2C} receptors inhibit accumbal and striatal DA release. (De Deurwaerdère <i>et al</i>, 2004) -DA necessary for active avoidance learning; 5-HT inhibits avoidance learning (Beninger, 1989) -DA reduces, 5-HT increases fatigue (Davis <i>et al</i>, 2000, Meeusen <i>et al</i>, 2006) -DA involved in appetite (engaging in behaviour); 5-HT involved in satiation (ending behaviour) (Berridge, 2007, Gruninger <i>et al</i>, 2007)
Collaborating	<ul style="list-style-type: none"> -Infusion of 5-HT in the nucleus accumbens increases DA levels and enhances responding (Sasaki-Adams and Kelley, 2001, Parsons and Justice, 1993) -Increased release of both 5-HT and DA in controllable punishment (Bland <i>et al</i>, 2003b) -5-HT_{2A} receptor activity linked to increased hyperactivity and impulsivity (Fletcher <i>et al</i>, 2002, 2007) -Antidepressant effect of boosting either 5-HT or DA (Hirschfeld, 1999, Nutt <i>et al</i>, 2007)
Neither	<ul style="list-style-type: none"> -Increased 5-HT in uncontrollable punishment (Bland <i>et al</i>, 2003b) -Neither DA nor 5-HT necessary for all forms of aversive contingency learning (Beninger, 1989)

Mechanism 4: Lurasidone effects on serotonergic receptors directly impacts on reward and penalty processing.

Based on electrophysiological recordings and imaging studies in rodents and primates, serotonergic neurons have been shown to directly impact upon reward (and predominantly aversive) processing (Bureau and Dayan, 2011; Cohen et al., 2015; Hayashi et al., 2015; Inaba et al., 2013; Li et al., 2016; Liu et al., 2014) as well as

avoidance behaviours (Boureau and Dayan, 2011; Crockett et al., 2012). For example, 5-HT neurons are activated (Grahn et al, 1999; Takase et al, 2004, 2005) and serotonin is released (Bland et al, 2003a) in the face of punishment (Lowry, 2002; Abrams et al, 2004). It is however, not clear from these studies if serotonin has an effect on learning as they did not dissociate learning from altered responsiveness to the valence of the reinforcing events themselves (Cools et al., 2008). A more recent study addressed this issue by explicitly separating neural learning signals from the receipt of outcomes per se (Scholl et al., 2017). They demonstrated that two week administration of SSRI citalopram enhanced reward and effort learning signals in a widespread brain network, including ACC, as well as more robust reward learning at the behavioural level. Their findings suggested that serotonin can modulate the ability to learn via a mechanism that is independent of stimulus valence and any increases to reward or effort outcome sensitivity per se.

Predictions of future punishment have a more complex effect on behaviour than prediction of rewards. This reflects a key difference or asymmetry between reward and penalties, where successful responses lead to repeated reward experience but avoided experience of penalty. Indeed, in the face of a proximal threat there is a choice of response – behavioural inhibition or active avoidance. The MID task simplifies the response to penalties, as it requires motivated fast responses on all trials (i.e. active avoidance). Whilst the serotonergic system may be more involved in inhibitory responses, the dopamine system seems to be more involved in the motivation and action responses to move away from the punisher. For example, inhibition of innate escape responses has been linked with 5-HT_{1A} (Deakin and Graeff, 1991; Misane et al, 1998), with decreasing 5-HT function facilitating active avoidance, and increasing 5-HT function impairing active avoidance learning (Archer, 1982; Archer et al, 1982). In contrast, accumbal DA release is associated with escape behaviour in response to a punisher and DA concentration and the phasic activity of other DA neurons (particularly in the meso-cortical pathway) increase in the face of aversion (Iordanova, 2009; Sorg and Kalivas, 1991; Guarraci and Kapp, 1999; Kiyatkin, 1988; Abercrombie et al, 1989; Louilot et al, 1986; Brischoux et al, 2009; Lammel et al, 2008; Matsumoto and Hikosaka, 2009). Therefore, in the context of our findings, one can speculate that lurasidone's action at 5-HT receptors could enhance 5-HT function,

thereby leading to inhibition of responses to salient win and loss cues and reducing BOLD signal during the anticipation phase.

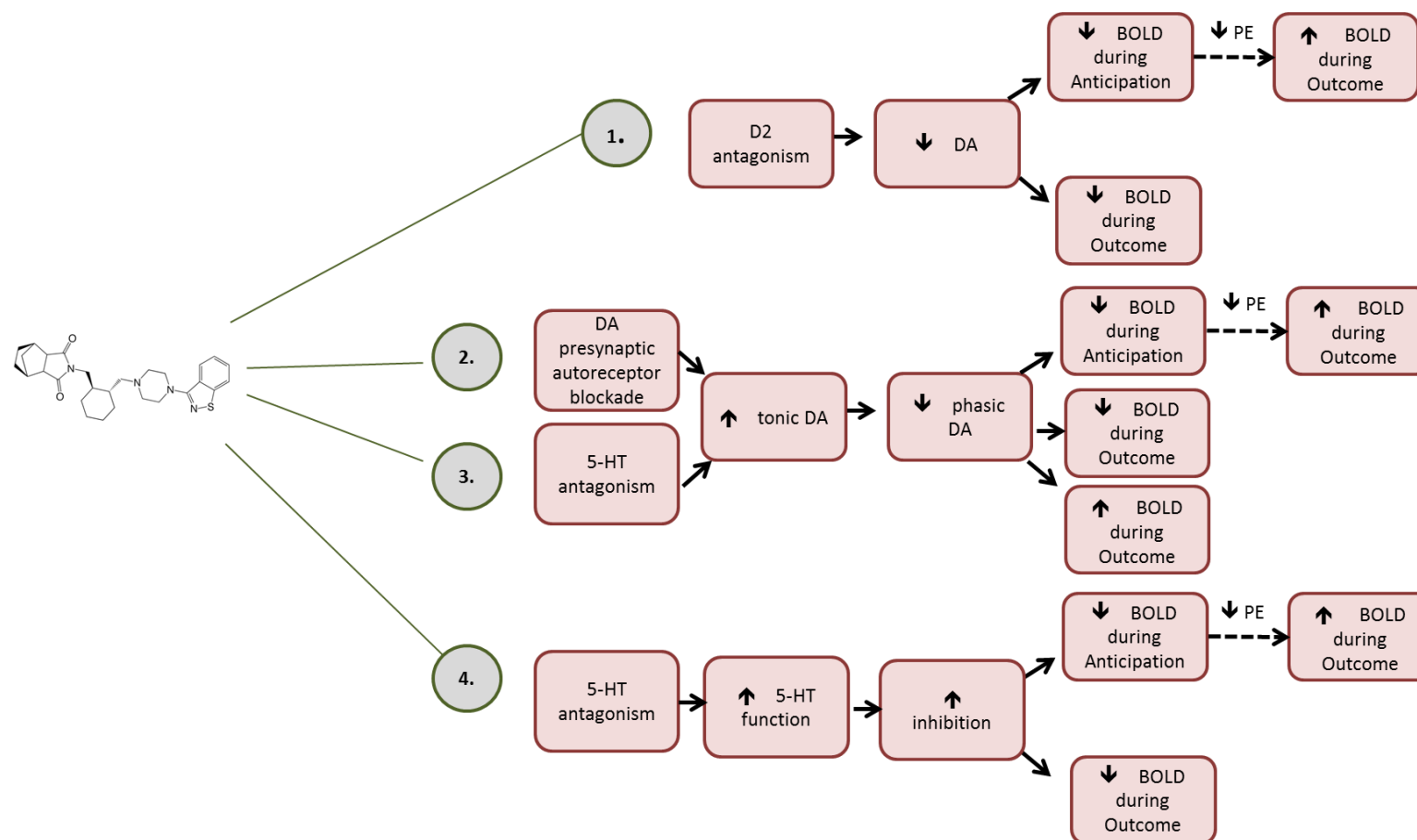


Figure 5.1. Schematic diagram illustrating four potential pathways in which lurasidone could act at dopamine (DA) D₂ and serotonin 5-HT receptors to elicit the results of this study: reduced striatal and ACC Blood-Oxygen-Level-Dependent (BOLD) activation to anticipation of both wins and losses and reduced responses to loss outcomes. PE= prediction error. Please refer to the text for detailed descriptions. BOLD response during outcomes could increase or decrease via two potential mechanisms. Lurasidone-induced increases in dopamine availability could reduce phasic DA firing of DA availability, subsequently reduce prediction error encoding, and thus increase BOLD response to (unexpected) outcomes in line with a Schultzian model of PE. Alternatively, lurasidone-induces increases in dopamine availability could decrease the phasic firing of dopamine neurons and the sensitivity of the dopamine reward system and lead to reduced BOLD signal for outcomes.

5.6.3 Summary of mechanisms

To summarise, changes in reward and penalty-related BOLD signal may be mediated by (i) direct modulation of tonic and phasic dopamine firing, (ii) indirect modulation of dopamine via serotonin or via interneurons or feedback loops involving other neurotransmitter systems and/or (iii) direct modulation of serotonergic neuron activity. These mechanisms may not necessarily be mutually exclusive and may interact with inter-individual and contextual factors that can alter baseline tonic firing, dopamine sensitisation and/or extracellular levels of dopamine (see Box 5.3).

There is a complex picture of the effects of pharmacological (D_2 antagonism) on reward and penalty processing. The effects may depend on (i) drug class (FGA (tight D_2 receptor binding) versus SGA (loose binding) (ii) pre- versus post-synaptic effects, which is related to (iii) drug dose and (iv) inter-individual variation (e.g. genetic variation which affects availability of dopamine receptors and regulators (DAT, COMT) that influence dopamine concentration and signaling. This may be complicated further by the fact that there is little knowledge about the function of phasic DA release in prefrontal regions (Bassareo and DiChiara, 1997; Sesack et al., 1998). Another issue is that there are distinct G protein-coupled dopamine receptor subtypes (Zawilska, 2003). In the tonic state of firing, neurons maintain a steady baseline level of dopamine and may predominantly target D_2 -like receptors which have higher affinity to dopamine (Richfield et al., 1989). In the phasic state, dopamine neurons sharply increase or decrease their bursting activity which leads to changes in dopaminergic availability in downstream neurons, and this is thought to mainly target D_1 -like receptors which have lower affinity to dopamine (Grieder et al., 2012). Moreover, striatal dopamine D_1 and D_2 receptors have opposing excitatory and inhibitory influences respectively. Thus, dopamine modulation can produce differing neuronal and BOLD related effects upstream depending on the context (Planert et al., 2013; Surmeier et al., 2007; Takahashi et al., 2010). At the same time, signals and neuromodulators from other cortical sites can alter the BOLD signal in a different direction to DA release (Ferenczi et al., 2016; Morita et al., 2012). Whilst simultaneously considering all of the above factors, one must also consider that blockade of one neurotransmitter system may lead to modulation of one or more other systems which can also influence BOLD signal.

Box 5.3. Inter-individual and contextual factors that can alter baseline tonic firing, dopamine sensitisation and/or extracellular levels of dopamine.

In line with this framework, I suggest that D_2 antagonism could primarily lead to reduced anticipatory responses (Figure 5.1), and lurasidone's impact on serotonergic receptors (Table 5.2) could primarily drive reduced responses to losses. This is

justified according to the above discussion. Inter-individual differences in receptor availability and binding potential between low and high depression severity subjects could account for the findings that lurasidone attenuated response to penalty outcomes in individuals with high depression severity only. Indeed, depression is associated with baseline differences in availability and function of 5-HT and/or D₂ receptors and reductions in binding relative to healthy volunteers (Sheline et al., 2004; Suhara et al., 1992; Yatham et al., 2005; Yatham et al., 1999). Thus, in accordance with previous findings that more divergent patterns of reward/penalty processing at baseline are associated with greater post-intervention change (Burkhouse et al., 2016; Rice et al., 2015; Vrieze et al., 2013b; Walsh et al., 2016), it could be that subjects with more severe depressive symptoms have more ‘room for improvement’ following lurasidone administration.

Another important consideration is the relationship or synchrony between the anticipatory and consummatory phases of reward and penalty processing, which I have mentioned in previous sections. The dominant model of striatal dopamine activity is that the salience or anticipatory activity predicts the outcome in cued-reward tasks (Schultz, 2016). In this context, any blunting in anticipatory processing or reduction in salience of cues with these drugs, could also affect outcome processing. Thus, beyond the interaction of several neurotransmitter systems, there may also be different effects of the drug across stages of reward and penalty processing. Indeed, as discussed in Introduction Section 1.2, reward and penalties show common and distinct activation patterns and the anticipation and consummatory phases of reward and penalty processing may be different systems. This supports a situation in which the administration of the same pharmacological agent could result in a divergent action of these neural systems when probed in the task. This has been shown in several studies of pharmacological manipulation of reward and penalty anticipatory and consummatory signals (Apitz and Bunzeck, 2014; Cavanagh et al., 2014; Evers et al., 2017; Wittmann and D'Esposito, 2015). Again, this is speculation, and the primary message is that there is a complex interaction between the major neurotransmitter

systems. Thus, it seems reasonable that the introduction of a drug that works at several receptors at once would have divergent effects.

5.7 Cerebral blood flow

It is notable, that in line with previous studies utilising dopamine antagonists (Goozee et al., 2014; Handley et al., 2013; Lahti et al., 2003; Lahti et al., 2005), we show here that lurasidone increased striatal cerebral blood flow at rest. Thus, our results add to the robust and consistent finding that single dose dopamine antagonists have potent effects in increasing striatal blood flow, and our novel finding is that this effect is equal across a spectrum of depression severity. Whereas our findings were exclusive to the putamen, some studies report significant decreases in perfusion in frontoparietal and occipital regions (Handley et al., 2013; Michels et al., 2016) and increases in CBF beyond the striatum, such as the supplementary motor area, insular and prefrontal cortex (Michels et al., 2016) with dopamine antagonists haloperidol, aripiprazole and quetiapine. Our findings are coherent with one study using a single oral dose of quetiapine which did not lead to CBF differences in the ACC, even at a liberal threshold of $p < .005$ (uncorrected) (Michels et al., 2016). However, it is worth noting that single dose haloperidol (3 mg) and aripiprazole (10 mg) increased rCBF in the ACC relative to placebo (Handley et al., 2013). Different patterns of rCBF modulation by these dopamine antagonists could reflect how their varying receptor affinity profiles alter (i) disinhibition of D_2 receptors (densely populated in the striatum) (Fernandez-Seara et al., 2011), (ii) astroglia (Attwell, et al., 2010), and (iii) serotonin receptors (densely populated in cortical regions) (Cohen et al., 1996).

Increases in blood flow following antipsychotic lurasidone administration may be related to increased neuronal metabolism in striatal areas due to the large density of D_2 receptors (Goozee et al., 2014), with blockade of D_2 receptors in the striatum potentially resulting in disinhibition of D_2 receptor-containing medium spiny neurons (Fernandez-Seara et al., 2011). Our results showed that the penalty and reward-related

findings were unchanged after controlling for baseline shifts in global and striatal CBF, and highlight the utility of multi-modal fMRI in identifying if the effects of the drug administered are indeed neuronal.

5.7.1 Interpretation of BOLD signal

There are four main points to emphasise for the interpretation of a modulation of BOLD changes by lurasidone. First, we must consider the complex nature of the BOLD signal representing the ultimate metabolic feed-forward signalling of complex circuits (Iannetti and Wise, 2007). As reviewed in the Imaging Methods Section (Chapter 2), change in BOLD does not unequivocally signify a similar change in direction in the integrative activity of neurons. In pharmacological fMRI, BOLD signal could change by either direct effects of the drug on neural activity or via non-specific effects on cerebral metabolic activity or on the vasculature itself (Iannetti and Wise, 2007; Wise and Tracey, 2006b). Thus, there could be convergent and divergent actions that lie behind the changes. Second, the fact that this thesis uses lurasidone, a drug with multiple targets (Figure 1.18), justifies the use of a technique that measures the ‘system level’ effect. This is because our key question is not whether the effects of dopamine or serotonin modulation affect reward and penalty processing but whether lurasidone affects these. Thus, a systems level approach for pharmacological MRI can be compared to other drugs. Third, and following on from this point, the addition of ASL significantly helps to narrow the interpretation of BOLD changes by precluding baseline changes in blood flow as an explanatory model. Thus, in the absence of non-specific effects, the most likely interpretation of the BOLD findings in this thesis is that lurasidone alters synaptic activity in the brain regions where there was a modulation effect (i.e. ACC for penalty outcomes and NAcc for reward outcomes). The baseline state as affected by increasing depression symptoms is important; however, how this baseline state affects the system is not well understood.

5.8 Implications for treatment

As mentioned throughout this thesis, the research on acute pharmacological interventions in reward and penalty processes in depression has direct implications for treatment. Experimental designs have the potential to further our understanding of the (causal) involvement of reward and penalty mechanisms in depression and define clear therapeutic targets. In this section, I discuss how the results from this thesis may inform treatment for depression.

5.8.1 Measurement of symptoms

Recognition and accurate measurement of emotional symptoms is undoubtedly vital for their effective and targeted treatment. The results from our study suggest that individuals with a greater number of depressive symptoms will have a stronger attenuation or ‘normalisation’ of penalty-related ACC activation when taking lurasidone. Individuals with greater alterations in the brain’s reward network may be better suited for interventions that target penalty-related functioning and related behaviours, whilst other interventions may be more affective to patients with different neural activity patterns. However, it is not possible to infer from these results if the suppression of an overactive negative salience system is therapeutic, and, longer term studies with regular symptom monitoring are needed to ascertain if this is the case. In this context, reliable and valid measurement tools are also indispensable for monitoring treatment progress and tailoring therapy according to patient profile. This concerns both traditional ways of testing treatment effectiveness, by using pre- and post-treatment measurement scales to evaluate symptom severity, and alternative approaches such as neuroimaging. It may be difficult to investigate the effect of a drug on emotional responses in depressed patients as some facets, such as loss of pleasure or anhedonia may persist even during clinical remission (Hasler et al., 2004; Hasler and Northoff, 2011). Moreover, as shown in this thesis and other studies, there may be changes in the neural correlates of reward and penalty processing before conscious appraisal or changes in behaviour. Therefore, brain markers may be more sensitive to assessing therapeutic response in the course of treatment and provide objective

measures of treatment progress (Dichter et al., 2011; Forbes et al., 2010). Moreover, neuroimaging may have implications for stratified or personalised medicine, where treatment is tailored towards the predominant symptomatology for an individual MDD patient (Korte et al., 2015) and to predict response to treatment. Indeed, other longitudinal studies have used a classification-based data analysis to demonstrate that if an early change in positive processing is not seen with antidepressant drug treatment, patients have little chance of responding to this later in the treatment course (Tranter et al., 2009). Having access to this information early on could help reduce multiple treatment cycles to identify an effective pharmacological therapy. Moreover, assessing pharmacological modulation of reward and penalty processing may help strategise combination treatments. In the context of this study, lurasidone reduced responses to penalties, but it remains to be determined whether the trend of potentiated responses to reward was non-significant because of a lack of power to detect a difference or because lurasidone's mechanism of action does not involve increasing responses to rewards further. If the latter explanation were to be the case, then it could help inform an optimal treatment strategy, for instance, by introducing a drug that promotes reward processing, which could be more beneficial than monotherapy. In a similar way, it provides the opportunity for psychological-pharmacological combination strategies, rather than putting two rational treatments together. For example, treatment could be optimised by introducing specific behavioural experiments at a time in which the individual may be most responsive to re-learning biases.

Whilst monitoring the course of treatment it may also be possible to identify early unwanted side effects of long-term treatment using neuroimaging methods. For example, SSRI treatment is associated with an experience of emotional constraint in which the emotional responses to both pleasurable and aversive experiences are diminished, or the salience of both rewarding and aversive stimuli is lost (McCabe et al., 2010; Opbroek et al., 2002; Price et al., 2009; Zald and Depue, 2001). Moreover, modest degrees of emotional blunting may be difficult for individuals to detect or report subjectively. Thus, brain imaging could provide a way to assess degrees of

emotional blunting by pharmacological treatment and assess if the therapeutic effect is in the ‘optimal’ direction of decreased responding to negativity, and increased responding to positivity.

Last of all, ASL appears particularly advantageous for treatment monitoring due to its very good test-retest reliability (Detre et al., 2012; Hermes et al., 2007; Hodkinson et al., 2013). However, it must be noted with all the above suggestions, that the associated costs of MR-techniques currently restrict its use in clinical practice.

5.9 Strengths, limitations and future avenues of research

The present thesis had several methodological and conceptual strengths. First, we tested the association between reward/penalty processing and depression using randomisation and experimental manipulation, thereby overcoming several of the limitations of correlational studies in drawing causal inferences. Indeed, acute pharmacological intervention designs, as used in this thesis, provide greater simplicity and specificity of findings, and greater experimental control than long-term pharmacopsychological interventions. Second, the cross-over, within-subject design affords higher statistical power than a parallel design by minimising subject variance as each individual acts as their own control, and increasing the drug variance. Third, we recruited medication-naïve subjects across the range of depression and anhedonia severity, thus avoiding the confound of medication (Abler et al., 2007; Pessiglione et al., 2006) and allowing us to assess the role of symptom level in reward processing on and off lurasidone. This research approach, which is in line with the Research Domain Criteria framework (Morris and Cuthbert, 2012) also does justice to findings concerning the genetic underpinnings of common mental illness (Plomin et al., 2009). Forth, our study has explored an important part of the literature which is the effects of an antidepressant on penalty-related processes, therefore demonstrating the importance

of examining for reward and penalty-related processes which have not been studied in conjunction enough. Fifth, our study addressed a key concern in pharmacimaging studies, namely that shifts in global or regional CBF could underlie changes observed in BOLD fMRI signal. By using arterial spin labelling, an imaging modality that allows the quantification of cerebral blood flow at rest, we could disentangle global and regional CBF changes from BOLD fMRI signal.

The thesis also had some conceptual and methodological limitations.

A potential conceptual issue is that we recruited unipolar patients, however, lurasidone has been licensed for use in bipolar depression (despite it also showing efficacy in depression with and without mixed features) (Suppes et al., 2016b). Given that bipolar depression may be related to a more readily activated striatal system (Satterthwaite et al., 2014), and perhaps higher baseline levels of dopamine relative to unipolar depression, the neuropsychological effects of lurasidone (D_2 antagonism in the striatum) in depressed bipolar patients may be different to the pattern found in this study which recruited sD and MDD cases. This warrants further investigation. Indeed, as excessive dopamine may underlie manic symptoms, it may be advantageous that lurasidone blocks D_2 receptors in the striatum to dampen dopamine signalling and prevent a manic switch. At the same time lurasidone dissociates rapidly from DA D_2 receptors (Fornaro et al., 2017) and its activity at 5-HT_{2A}, 5-HT_{1A} and 5-HT₇ increases DA levels (Huang et al., 2012; Yatham et al., 2005). This may ensure a sufficient and permanent input of striatal dopamine to maintain drive and affective responsivity (Juckel, 2016; Juckel et al., 2006). Thus, it has been suggested that a regionally selective balance of dopamine D_2 antagonism and serotonin 5-HT_{2A} antagonism may be the key to stabilising mood in bipolar depression.

Second, our study was not designed to capture changes in depressive symptoms following lurasidone and therefore it is unclear how these would correlate with brain responses. The next piece of information which would be needed to infer causality, is whether lurasidone-induced neural changes (reduced penalty-related ACC signalling and increased reward-related NAcc signalling) predict a decline in depressive and

anhedonic symptoms (e.g. Godlewska et al., 2016; Shiroma et al., 2014; Tranter et al., 2009). This would require longer-term lurasidone treatment in longitudinal studies with assessment of pre-post changes in behavioural and neural responses. If behavioural and neural responses could be collected at several time points it would also be fascinating to explore whether the findings fit a behavioural activation model. This would predict a normalisation of responses to outcomes (consummation), prior to a normalisation of neural anticipatory signals with longer term antidepressant treatment (Dimidjian et al., 2011). Thus, a general direction for future research would be to further elucidate how lurasidone's mechanism of action links to the cognitive neuropsychological model of antidepressant action (Harmer et al., 2009a). However, our strategy of searching for the signal of an intervention in the first place is consistent with current recommendations to boost drug discovery (Krystal and State, 2014).

As reviewed in Section 1.6.3.7 (Table 1.9), there are a number of challenges when investigating the pharmacological manipulation of reward and penalty processing. Our study did not address some of the potential sources of noise or confounding which affect the dynamics of drug response. Factors known to vary dopamine baseline levels and should ideally be controlled when assessing response to dopaminergic modulation include sex, menstrual cycle (Dreher et al., 2007; Jacobs and D'Esposito, 2011), and genetic variants (catechol-O-methyl transferase (COMT) Val(158)Met polymorphism, MET/MET, VAL/VAL, VAL/MET (Wichers et al., 2008)). Indeed, more knowledge about individual genetic and biological variation in association with reward processing may add to the process of prediction and improvement of treatment response to antidepressant medication. Quantitative measures of dopamine baseline levels (e.g. PET neuroimaging, eye-blink rate) could also be a useful tool. However, a recent study found that spontaneous eye blink rate is uncorrelated with dopamine D₂ receptor availability and unmodulated by dopamine agonism, thereby suggesting caution in using EBR as a proxy for dopamine function in healthy humans (Dang et al., 2017). Overall, this study would have been greatly improved by an interdisciplinary pharmacogenetics-neuroimaging-behavioural approach (Jongkees and Colzato, 2016).

A pressing limitation is the reward (MID task) paradigm used in the current study. Monetary reward may not be the prime incentive for all people, nor most fundamental to human functioning, and it is uncertain whether another paradigm related to life tasks in our sample age (social peer rewards, achievement success) may result in even clearer findings on reward and penalty dysfunction in depression. Future studies should explore a wider array of reward tasks, such as the use of positive social stimuli during reward anticipation (e.g. Smoski et al., 2011), combined with ecological monitoring of everyday experiences, to elucidate mechanisms more fundamentally tied to the deficits found in depression and anhedonia. A minor, but potentially important detail for the analysis of the outcome phase is the fact that a running total of the amount currently won was displayed on all trials (neutral, win, no win, loss and avoided loss feedback); and this stimulus may be inherently rewarding. This could have diminished or confound the contrast of win and loss trial types relative to the neutral trial. However, we avoided this in our analyses by comparing win>no win and loss>avoided loss outcomes. Nevertheless, these limits must be seen in the context of the advantages of using this task which include its excellent test-retest reliability (Plichta et al., 2012; Wu et al., 2014) and the fact that it is one of the most widely used and validated paradigms, thereby allowing for comparisons across studies and phases of reward processing.

The mass-univariate analytical approach and ROI analysis adopted in the current study may have also been restrictive. Focusing on individual regions (functional specialisation), largely ignores the nature of the reward *network* (functional integration). Thus, connectivity analyses (e.g. Gabbay et al., 2013) and machine learning may provide additional insights into changes in the relationship between subcortical and cortical regions across normal and MDD development. Indeed, a previous study by Admon et al., (2017) utilised psychophysiological interaction (PPI) analyses to probe group differences in connectivity separately in response to positive and negative outcomes (i.e. monetary gains and penalties) in the MID task. PPI is a method to examine whether the correlation in activity between two spatially remote brain regions is different in different psychological contexts (i.e. whether there is an

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interaction between the psychological state and the functional coupling between two brain areas). The task used in the current study was not optimal for PPI analyses as it was an event-related design with relatively short stimulus durations and less volumes per condition (26 trials per condition) relative to other MID tasks designed for PPI analyses (e.g. 45 trials per condition in Admon et al., (2017)). These two characteristics may have led to issues of co-activation and an underpowered analysis (i.e. reliably making inferences that a seed region is correlated with another given area with a similar signal) (Poldrack et al., 2011). Another fruitful approach would have been to explore the conceptualisation of hedonic capacity in MDD as a decreased capacity to *sustain* response to rewards over time (Heller et al., 2013; Pizzagalli et al., 2008c). In line with previous studies (Carl et al., 2016b; Walsh et al., 2016), we could have examined depression and medication effects on the change in neural activity to reward and penalty outcomes across two runs of the MID task (i.e. sustained or attenuated activity over time), as opposed to aggregating across the two runs (i.e. global responses). Indeed, a previous study showed greater sensitivity in predicting clinical response to treatment in MDD patients when examining patterns of neural attenuation compared to global values. This suggests the importance of examining temporal changes in neural activity as an MDD endophenotype that is relevant for predicting antidepressant response (Walsh et al., 2016).

An important issue which I have already discussed in 5.4.3 is the suitability of the MID for PE analyses. This is because the parameters of the task were pre-learned and reward prediction error (RPE; i.e. the presentation of an unexpected reward or omission of an expected reward) would not occur in its simplest sense. Thus, other paradigms may have been more suited to eliciting and manipulating PEs.

Nevertheless, the analytical framework for PE encoding used in this thesis was based on prior MID PE analysis (Staudinger et al., 2009) and an effort was made to control for factors that influence the analysis (e.g. equal numbers of each type of trial within each outcome). If this study could be completed again, I would include an offline behavioural task such as the probabilistic reward learning task used by Admon et al.,

(2017) to assess the impact of medication and depression on reward and penalty-related learning.

Finally, there were also some potential issues with the ROIs chosen in this study. First, ACC boundaries have no anatomical derivation and are not based on standard views of separation of regions (Haber and Behrens, 2014). Second, the use of small regions and bounded regions assumes excellent coregistration and normalisation. Third, the amygdala and NAcc are at risk of being offset by co-registration biases (caused by highly informative regions dominating the difference measures). These do not invalidate the ROIs chosen but do indicate that methods such as Feesurfer 6 registrations (<http://surfer.nmr.mgh.harvard.edu/>) may be better for summarising activation in these structures as their validation is proving to be excellent (Han et al., 2006; Reuter et al., 2012). Nevertheless, we attempted to minimise these issues by (i) testing different co-registration and normalisation approaches and using the best method (See Methods Section 3.8.2); (ii) examining ROI overlap in each participant and across both sessions (good overlap, data available upon request) and (iii) confirming that the peaks of activation in the regions fell within the ROIs.

5.10 Overall Conclusion

The work presented in this thesis has shown for the first time the effect of acute dose lurasidone on the neural correlates of reward and penalty-related processing and prediction error in depression. Lurasidone transiently decreased penalty-related ACC activity and PE in individuals with high symptoms of depression and increased reward-related striatal activity in individuals with elevated anhedonic symptoms. Importantly, these findings were not altered by co-occurring anxiety symptoms, self-reported changes in sedation and state anxiety or increased striatal CBF under lurasidone. Modulation of dopamine and serotonin transmission (at dopamine D₂ and serotonin 5-HT_{1A}, 5-HT_{2A}, and 5-HT₇ receptors) may help to normalise processing of negative and positive outcomes in depressed individuals through the alteration of ACC

and NAcc signalling respectively. Further work is needed to elucidate whether lurasidone reduces *encoding* of penalty-related *PE* or hypersensitive *experiences* to negative feedback in depression. Yet, lurasidone may potentiate pleasure *experience*, as opposed to reward learning in individuals with elevated anhedonia. Taken together, the thesis brings increased knowledge and precision to our understanding of abnormalities in neural reward-penalty systems across the continuum of depression and anhedonia severity and highlights the potential of targeted pharmacological treatments to normalise these processes. In particular, ACC and NAcc signalling may provide a new target for engagement in future drug development studies. Using an experimental medicine design such as the one used in this thesis, whilst accounting for vascular effects, could help identify relevant compounds which could then be tested further in using longer-term follow up. Moreover, studies exploring more precise facets of reward and penalty processing with appropriate tasks probing specifically PE could provide understanding of the systems-level operations of dopamine antagonists, and afford knowledge required to develop effective new compounds and improve clinical outcomes.

References

- Abler, Erk, S., Walter, H., 2007. Human reward system activation is modulated by a single dose of olanzapine in healthy subjects in an event-related, double-blind, placebo-controlled fMRI study. *Psychopharmacology* 191, 823-833.
- Abler, Walter, H., Erk, S., Kammerer, H., Spitzer, M., 2006. Prediction error as a linear function of reward probability is coded in human nucleus accumbens. *NeuroImage* 31, 790-795.
- Abler, B., Gron, G., Hartmann, A., Metzger, C., Walter, M., 2012. Modulation of Frontostriatal Interaction Aligns with Reduced Primary Reward Processing under Serotonergic Drugs. *Journal of Neuroscience* 32, 1329-1335.
- Abler, B., Seeringer, A., Hartmann, A., Groen, G., Metzger, C., Walter, M., Stingl, J., 2011. Neural Correlates of Antidepressant-Related Sexual Dysfunction: A Placebo-Controlled fMRI Study on Healthy Males Under Subchronic Paroxetine and Bupropion. *Neuropsychopharmacology* 36, 1837-1847.
- Admon, Kaiser, R.H., Dillon, D.G., Beltzer, M., Goer, F., Olson, D.P., Vitaliano, G., Pizzagalli, D.A., 2017. Dopaminergic Enhancement of Striatal Response to Reward in Major Depression. *American Journal of Psychiatry* 174, 378-386.
- Admon, Nickerson, L.D., Dillon, D.G., Holmes, A.J., Bogdan, R., Kumar, P., Dougherty, D.D., Iosifescu, D.V., Mischoulon, D., Fava, M., Pizzagalli, D.A., 2015a. Dissociable cortico-striatal connectivity abnormalities in major depression in response to monetary gains and penalties. *Psychol Med* 45, 121-131.
- Aguirre, G.K., Detre, J.A., 2012. The development and future of perfusion fMRI for dynamic imaging of human brain activity. *NeuroImage* 62, 1279-1285.
- Aguirre, G.K., Detre, J.A., Wang, J.J., 2005. Perfusion fMRI for functional neuroimaging. *Neuroimaging, Pt A* 66, 213-236.
- Alexander, W.H., Brown, J.W., 2011. Medial prefrontal cortex as an action-outcome predictor. *Nature Neuroscience* 14, 1338-U1163.

- Alsop, D.C., Detre, J.A., Golay, X., Gunther, M., Hendrikse, J., Hernandez-Garcia, L., Lu, H.Z., MacIntosh, B.J., Parkes, L.M., Smits, M., van Osch, M.J.P., Wang, D.J.J., Wong, E.C., Zaharchuk, G., 2015. Recommended Implementation of Arterial Spin-Labeled Perfusion MRI for Clinical Applications: A Consensus of the ISMRM Perfusion Study Group and the European Consortium for ASL in Dementia. *Magnetic Resonance in Medicine* 73, 102-116.
- Ambrosini, P.J., Metz, C., Bianchi, M.D., Rabinovich, H., Undie, A., 1991. Concurrent Validity And Psychometric Properties Of The Beck Depression Inventory In Outpatient Adolescents. *Journal of the American Academy of Child and Adolescent Psychiatry* 30, 51-57.
- Angold, A., Costello, E.J., Messer, S.C., Pickles, A., 1995. Development of a short questionnaire for use in epidemiological studies of depression in children and adolescents. Dec 1995. *International Journal of Methods in Psychiatric Research* 5, pp.
- Angst, J., Sellar, R., Merikangas, K.R., 2000. Depressive spectrum diagnoses. *Comprehensive Psychiatry* 41, 39-47.
- Anisman, H., Irwin, J., Sklar, L.S., 1979. Deficits Of Escape Performance Following Catecholamine Depletion - Implications For Behavioral Deficits Induced By Uncontrollable Stress. *Psychopharmacology* 64, 163-170.
- Apitz, T., Bunzeck, N., 2014. Early Effects of Reward Anticipation Are Modulated by Dopaminergic Stimulation. *PLoS ONE* 9.
- Argyropoulos, S.V., Nutt, D.J., 2013. Anhedonia revisited: is there a role for dopamine-targeting drugs for depression? *Journal of Psychopharmacology* 27, 869-877.
- Arnone, D., Horder, J., Cowen, P.J., Harmer, C.J., 2009. Early effects of mirtazapine on emotional processing. *Psychopharmacology* 203, 685-691.
- Arroll, B., Elley, C.R., Fishman, T., Goodyear-Smith, F.A., Kenealy, T., Blashki, G., Kerse, N., MacGillivray, S., 2009. Antidepressants versus placebo for depression in primary care. *Cochrane Database of Systematic Reviews*.
- Arrondo, G., Segarra, N., Metastasio, A., Ziauddeen, H., Spencer, J., Reinders, N.R., Dudas, R.B., Robbins, T.W., Fletcher, P.C., Murray, G.K., 2015. Reduction in

- ventral striatal activity when anticipating a reward in depression and schizophrenia: a replicated cross-diagnostic finding. *Front Psychol* 6, 1280.
- Ashburner, J., Barnes, G., Chen, C., Daunizeau, J., Flandin, G., Friston, K., Kiebel, S., Kilner, J., Litvak, V., Moran, R., 2014. SPM12 manual. London: Wellcome Trust.
- Ayuso-Mateos, J.L., Nuevo, R., Verdes, E., Naidoo, N., Chatterji, S., 2010. From depressive symptoms to depressive disorders: the relevance of thresholds. *The British Journal of Psychiatry* 196, 365-371.
- Balazs, J., Miklosi, M., Keresztesy, A., Hoven, C.W., Carli, V., Wasserman, C., Apter, A., Bobes, J., Brunner, R., Cosman, D., Cotter, P., Haring, C., Iosue, M., Kaess, M., Kahn, J.P., Keeley, H., Marusic, D., Postuvan, V., Resch, F., Saiz, P.A., Sisask, M., Snir, A., Tubiana, A., Varnik, A., Sarchiapone, M., Wasserman, D., 2013. Adolescent subthreshold-depression and anxiety: psychopathology, functional impairment and increased suicide risk. *J Child Psychol Psychiatry* 54, 670-677.
- Ban, T.A., 2006. The role of serendipity in drug discovery. *Dialogues Clin Neurosci* 8, 335-344.
- Banaschewski, T., Brandeis, D., 2007. Annotation: What electrical brain activity tells us about brain function that other techniques cannot tell us - a child psychiatric perspective. *Journal of Child Psychology and Psychiatry* 48, 415-435.
- Bar-Haim, Y., Lamy, D., Pergamin, L., Bakermans-Kranenburg, M.J., van Ijzendoorn, M.H., 2007. Threat-related attentional bias in anxious and nonanxious individuals: A meta-analytic study. *Psychological Bulletin* 133, 1-24.
- Barrera, M., Garrisonjones, C.V., 1988. Properties Of The Beck Depression Inventory As A Screening Instrument For Adolescent Depression. *Journal of Abnormal Child Psychology* 16, 263-273.
- Bartra, O., McGuire, J.T., Kable, J.W., 2013. The valuation system: a coordinate-based meta-analysis of BOLD fMRI experiments examining neural correlates of subjective value. *NeuroImage* 76, 412-427.
- Bassareo, V., DiChiara, G., 1997. Differential influence of associative and nonassociative learning mechanisms on the responsiveness of prefrontal and

- accumbal dopamine transmission to food stimuli in rats fed ad libitum. *Journal of Neuroscience* 17, 851-861.
- Bauer, M., Bschor, T., Pfennig, A., Whybrow, P.C., Angst, J., Versiani, M., Möller, H.-J., Disorders, W.T.F.o.U.D., Bauer, M., Bschor, T., 2007. World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for biological treatment of unipolar depressive disorders in primary care. *The World Journal of Biological Psychiatry* 8, 67-104.
- Baxter, M.G., Murray, E.A., 2002. The amygdala and reward. *Nature Reviews Neuroscience* 3, 563-573.
- Bechara, A., Damasio, A.R., Damasio, H., Anderson, S.W., 1994. Insensitivity to future consequences following damage to human prefrontal cortex. *Cognition* 50, 7-15.
- Beck, A.T., 2008. The evolution of the cognitive model of depression and its neurobiological correlates. *American Journal of Psychiatry* 165, 969-977.
- Beck, A.T., Steer, R.A., Ball, R., Ranieri, W.F., 1996. Comparison of Beck Depression Inventories-IA and -II in psychiatric outpatients. *Journal of Personality Assessment* 67, 588-597.
- Beck, C.A., Patten, S.B., 2004. Adjustment to antidepressant utilization rates to account for depression in remission. *Comprehensive Psychiatry* 45, 268-274.
- Beierholm, U., Guitart-Masip, M., Economides, M., Chowdhury, R., Duezel, E., Dolan, R., Dayan, P., 2013. Dopamine Modulates Reward-Related Vigor. *Neuropsychopharmacology* 38, 1495-1503.
- Berridge, K.C., 2007. The debate over dopamine's role in reward: the case for incentive salience. *Psychopharmacology* 191, 391-431.
- Berridge, K.C., Kringelbach, M.L., 2008. Affective neuroscience of pleasure: reward in humans and animals. *Psychopharmacology* 199, 457-480.
- Berridge, K.C., Kringelbach, M.L., 2015. Pleasure systems in the brain. *Neuron* 86, 646-664.
- Berridge, K.C., Robinson, T.E., Aldridge, J.W., 2009. Dissecting components of reward: 'liking', 'wanting', and learning. *Curr Opin Pharmacol* 9, 65-73.

- Berridge, K.C., Venier, I.L., Robinson, T.E., 1989. Taste Reactivity Analysis Of 6-Hydroxydopamine-Induced Aphagia - Implications For Arousal And Anhedonia Hypotheses Of Dopamine Function. *Behavioral Neuroscience* 103, 36-45.
- Bertha, E.A., Balazs, J., 2013. Subthreshold depression in adolescence: a systematic review. *Eur Child Adolesc Psychiatry* 22, 589-603.
- Bessa, J.M., Ferreira, D., Melo, I., Marques, F., Cerqueira, J.J., Palha, J.A., Almeida, O.F.X., Sousa, N., 2009a. Hippocampal neurogenesis induced by antidepressant drugs: an epiphenomenon in their mood-improving actions. *Molecular Psychiatry* 14, 739 1359-4184.
- Bessa, J.M., Ferreira, D., Melo, I., Marques, F., Cerqueira, J.J., Palha, J.A., Almeida, O.F.X., Sousa, N., 2009b. The mood-improving actions of antidepressants do not depend on neurogenesis but are associated with neuronal remodeling. *Molecular Psychiatry* 14, 764 1476-5578.
- Bissonette, G.B., Gentry, R.N., Padmala, S., Pessoa, L., Roesch, M.R., 2014. Impact of appetitive and aversive outcomes on brain responses: linking the animal and human literatures. *Frontiers in Systems Neuroscience* 8, 24-24.
- Black, K.J., Piccirillo, M.L., Koller, J.M., Hsieh, T., Wang, L., Mintun, M.A., 2015. Levodopa effects on [(11)C]raclopride binding in the resting human brain. *F1000Res* 4, 23.
- Blink, E., 2004. Basic MRI physics. *MRI physics*.
- Boissier, J.R., Pagny, J., 1960. [Pharmacodynamic study of a new important neuroleptic: haloperidol (R-1625). I. Toxicity. Its potentiator action in anesthesia and analgesia]. *Therapie* 15, 479-487.
- Boksem, M.A.S., Tops, M., Kostermans, E., De Cremer, D., 2008. Sensitivity to punishment and reward omission: Evidence from error-related ERP components. *Biological Psychology* 79, 185-192.
- Bolstad, I., Andreassen, O.A., Groote, I., Server, A., Sjaastad, I., Kapur, S., Jensen, J., 2015. Effects of haloperidol and aripiprazole on the human mesolimbic motivational system: A pharmacological fMRI study. *European Neuropsychopharmacology* 25, 2252-2261.

- Bond, A.J., James, D.C., Lader, M.H., 1974a. Physiological And Psychological Measures In Anxious Patients. *Psychological Medicine* 4, 364-373.
- Bond, A.J., James, D.C., Lader, M.H., 1974b. Sedative Effects On Physiological And Psychological Measures In Anxious Patients. *Psychological Medicine* 4, 374-380.
- Boschen, S.L., Wietzikoski, E.C., Winn, P., Da Cunha, C., 2011. The role of nucleus accumbens and dorsolateral striatal D2 receptors in active avoidance conditioning. *Neurobiology of Learning and Memory* 96, 254-262.
- Bossong, M.G., Jager, G., van Hell, H.H., Zuurman, L., Jansma, J.M., Mehta, M.A., van Gerven, J.M.A., Kahn, R.S., Ramsey, N.F., 2012. Effects of Δ^9 -tetrahydrocannabinol administration on human encoding and recall memory function: a pharmacological fMRI study. *Journal of Cognitive Neuroscience* 24, 588-599.
- Boureau, Y.L., Dayan, P., 2011. Opponency Revisited: Competition and Cooperation Between Dopamine and Serotonin. *Neuropsychopharmacology* 36, 74-97.
- Bress, J.N., Foti, D., Kotov, R., Klein, D.N., Hajcak, G., 2013. Blunted neural response to rewards prospectively predicts depression in adolescent girls. *Psychophysiology* 50, 74-81.
- Bress, J.N., Meyer, A., Hajcak, G., 2015a. Differentiating anxiety and depression in children and adolescents: evidence from event-related brain potentials. *J Clin Child Adolesc Psychol* 44, 238-249.
- Bress, J.N., Meyer, A., Proudfit, G.H., 2015b. The stability of the feedback negativity and its relationship with depression during childhood and adolescence. *Dev Psychopathol* 27, 1285-1294.
- Bress, J.N., Smith, E., Foti, D., Klein, D.N., Hajcak, G., 2012. Neural response to reward and depressive symptoms in late childhood to early adolescence. *Biol Psychol* 89, 156-162.
- Briand, L.A., Gritton, H., Howe, W.M., Young, D.A., Sarter, M., 2007. Modulators in concert for cognition: Modulator interactions in the prefrontal cortex. *Prog Neurobiol* 83, 69-91.

- Brugha, T., Jenkins, R., Bebbington, P., Meltzer, H., Lewis, G., Farrell, M., 2004. Risk factors and the prevalence of neurosis and psychosis in ethnic groups in Great Britain. *Soc Psychiatry Psychiatr Epidemiol* 39, 939-946.
- Brugue, E., Vieta, E., 2007. Atypical antipsychotics in bipolar depression: Neurobiological basis and clinical implications. *Progress in Neuro-Psychopharmacology & Biological Psychiatry* 31, 275-282.
- Buchel, C., Dolan, R.J., Armony, J.L., Friston, K.J., 1999. Amygdala-hippocampal involvement in human aversive trace conditioning revealed through event-related functional magnetic resonance imaging. *Journal of Neuroscience* 19, 10869-10876.
- Buchel, C., Morris, J., Dolan, R.J., Friston, K.J., 1998. Brain systems mediating aversive conditioning: an event-related fMRI study. *Neuron* 20, 947-957.
- Burkhouse, K.L., Kujawa, A., Kennedy, A.E., Shankman, S.A., Langenecker, S.A., Phan, K.L., Klumpp, H., 2016. Neural Reactivity To Reward As A Predictor Of Cognitive Behavioral Therapy Response In Anxiety And Depression. *Depression and Anxiety* 33, 281-288.
- Byrne, K.A., Norris, D.D., Worthy, D.A., 2016. Dopamine, depressive symptoms, and decision-making: the relationship between spontaneous eye blink rate and depressive symptoms predicts Iowa Gambling Task performance. *Cogn Affect Behav Neurosci* 16, 23-36.
- Campbell, D.T., Fiske, D.W., 1959. Convergent and discriminant validation by the multitrait-multimethod matrix. *Psychological Bulletin* 56, 81 1939-1455.
- Canals, J., Blade, J., Carbajo, G., Domenech-Llaberia, E.D., 2001. The Beck Depression Inventory: Psychometric characteristics and usefulness in nonclinical adolescents. *European Journal of Psychological Assessment* 17, 63-68.
- Carl, H., Walsh, E., Eisenlohr-Moul, T., Minkel, J., Crowther, A., Moore, T., Gibbs, D., Petty, C., Bizzell, J., Dichter, G.S., Smoski, M.J., 2016a. Sustained anterior cingulate cortex activation during reward processing predicts response to psychotherapy in major depressive disorder. *J Affect Disord* 203, 204-212.

- Carlson, J.M., Foti, D., Mujica-Parodi, L.R., Harmon-Jones, E., Hajcak, G., 2011. Ventral striatal and medial prefrontal BOLD activation is correlated with reward-related electrocortical activity: a combined ERP and fMRI study. *Neuroimage* 57, 1608-1616.
- Carvalho, A.F., Machado, J.R., Cavalcante, J.L., 2009. Augmentation strategies for treatment-resistant depression. *Current Opinion in Psychiatry* 22, 7-12.
- Casement, M.D., Guyer, A.E., Hipwell, A.E., McAloon, R.L., Hoffmann, A.M., Keenan, K.E., Forbes, E.E., 2014. Girls' challenging social experiences in early adolescence predict neural response to rewards and depressive symptoms. *Developmental Cognitive Neuroscience* 8, 18-27.
- Casey, B.J., Jones, R.M., 2010. Neurobiology of the Adolescent Brain and Behavior: Implications for Substance Use Disorders. *Journal of the American Academy of Child and Adolescent Psychiatry* 49, 1189-1201.
- Caspi, A., Houts, R.M., Belsky, D.W., Goldman-Mellor, S.J., Harrington, H., Israel, S., Meier, M.H., Ramrakha, S., Shalev, I., Poulton, R., 2014. The p factor: one general psychopathology factor in the structure of psychiatric disorders? *Clinical Psychological Science* 2, 119-137.
- Cavanagh, J.F., Masters, S.E., Bath, K., Frank, M.J., 2014. Conflict acts as an implicit cost in reinforcement learning. *Nat Commun* 5, 5394.
- Cella, M., Dymond, S., Cooper, A., 2010. Impaired flexible decision-making in Major Depressive Disorder. *J Affect Disord* 124, 207-210.
- Challis, C., Berton, O., 2015. Top-Down Control of Serotonin Systems by the Prefrontal Cortex: A Path toward Restored Socioemotional Function in Depression. *Acs Chemical Neuroscience* 6, 1040-1054.
- Chapman, A.L., Lynch, T.R., Rosenthal, M.Z., Cheavens, J.S., Smoski, M.J., Krishnan, K.R.R., 2007. Risk aversion among depressed older adults with obsessive compulsive personality disorder. *Cognitive Therapy and Research* 31, 161-174.
- Chase, H.W., Frank, M.J., Michael, A., Bullmore, E.T., Sahakian, B.J., Robbins, T.W., 2010. Approach and avoidance learning in patients with major depression and healthy controls: relation to anhedonia. *Psychological Medicine* 40, 433-440.

- Chen, J., Lipska, B.K., Halim, N., Ma, Q.D., Matsumoto, M., Melhem, S., Kolachana, B.S., Hyde, T.M., Herman, M.M., Apud, J., Egan, M.F., Kleinman, J.E., Weinberger, D.R., 2004. Functional analysis of genetic variation in catechol-O-methyltransferase (COMT): effects on mRNA, protein, and enzyme activity in postmortem human brain. *Am J Hum Genet* 75, 807-821.
- Chen, Y., Wang, J., Korczykowski, M., Fernandez-Seara, M., Detre, J.A., 2010. Comparison of reproducibility between continuous, pulsed, and pseudo-continuous arterial spin labeling. p. 4078.
- Childs, E., de Wit, H., 2013. Contextual conditioning enhances the psychostimulant and incentive properties of d-amphetamine in humans. *Addict Biol* 18, 985-992.
- Choi, J.-K., Chen, Y.I., Hamel, E., Jenkins, B.G., 2006. Brain hemodynamic changes mediated by dopamine receptors: role of the cerebral microvasculature in dopamine-mediated neurovascular coupling. *NeuroImage* 30, 700-712.
- Chowdhury, R., Guitart-Masip, M., Lambert, C., Dayan, P., Huys, Q., Duezel, E., Dolan, R.J., 2013a. Dopamine restores reward prediction errors in old age. *Nature Neuroscience* 16, 648.
- Chua, P., Krams, M., Toni, I., Passingham, R., Dolan, R., 1999. A functional anatomy of anticipatory anxiety. *NeuroImage* 9, 563-571.
- Cipriani, A., Furukawa, T.A., Salanti, G., Chaimani, A., Atkinson, L.Z., Ogawa, Y., Levcht, S., Ruhe, H.G., Turner, E.H., Higgins, J.P.T., Egger, M., Takeshima, N., Hayasaka, Y., Imai, H., Shinohara, K., Tajika, A., Ioannidis, J.P.A., Geddes, J.R., 2018. Comparative efficacy and acceptability of 21 antidepressant drugs for the acute treatment of adults with major depressive disorder: a systematic review and network meta-analysis. *Lancet* 391, 1357-1366.
- Cipriani, A., Furukawa, T.A., Salanti, G., Geddes, J.R., Higgins, J.P.T., Churchill, R., Watanabe, N., Nakagawa, A., Omori, I.M., McGuire, H., Tansella, M., Barbui, C., 2009. Comparative efficacy and acceptability of 12 new-generation antidepressants: a multiple-treatments meta-analysis. *Lancet* 373, 746-758.

- Citri, A., Malenka, R.C., 2008. Synaptic plasticity: Multiple forms, functions, and mechanisms. *Neuropsychopharmacology* 33, 18-41.
- Citrome, L., Ketter, T.A., Cucchiaro, J., Loebel, A., 2014. Clinical assessment of lurasidone benefit and risk in the treatment of bipolar I depression using number needed to treat, number needed to harm, and likelihood to be helped or harmed. *Journal of Affective Disorders* 155, 20-27.
- Clarke, H.F., Robbins, T.W., Roberts, A.C., 2008. Lesions of the Medial Striatum in Monkeys Produce Perseverative Impairments during Reversal Learning Similar to Those Produced by Lesions of the Orbitofrontal Cortex. *Journal of Neuroscience* 28, 10972-10982.
- Cleare, A., Pariante, C.M., Young, A.H., Anderson, I.M., Christmas, D., Cowen, P.J., Dickens, C., Ferrier, I.N., Geddes, J., Gilbody, S., Haddad, P.M., Katona, C., Lewis, G., Malizia, A., McAllister-Williams, R.H., Ramchandani, P., Scott, J., Taylor, D., Uher, R., British Assoc, P., 2015. Evidence-based guidelines for treating depressive disorders with antidepressants: A revision of the 2008 British Association for Psychopharmacology guidelines. *Journal of Psychopharmacology* 29, 459-525.
- Clery-Melin, M.-L., Schmidt, L., Lafargue, G., Baup, N., Fossati, P., Pessiglione, M., 2011. Why Don't You Try Harder? An Investigation of Effort Production in Major Depression. *PLoS ONE* 6.
- Cohen, J.Y., Amoroso, M.W., Uchida, N., 2015. Serotonergic neurons signal reward and punishment on multiple timescales. *Elife* 4.
- Cohen, J.Y., Haesler, S., Vong, L., Lowell, B.B., Uchida, N., 2012. Neuron-type-specific signals for reward and punishment in the ventral tegmental area. *Nature* 482, 85-U109.
- Cohen, M.X., Krohn-Grimberghe, A., Elger, C.E., Weber, B., 2007. Dopamine gene predicts the brain's response to dopaminergic drug. *Eur J Neurosci* 26, 3652-3660.
- Cohen, M.X., Young, J., Baek, J.-M., Kessler, C., Ranganath, C., 2005. Individual differences in extraversion and dopamine genetics predict neural reward responses. *Brain research. Cognitive brain research* 25, 851-861.

- Cohen, Z., Bonvento, G., Lacombe, P., Hamel, E., 1996. Serotonin in the regulation of brain microcirculation. *Prog Neurobiol* 50, 335-348.
- Collins, A.G.E., Frank, M.J., 2016. Surprise! Dopamine signals mix action, value and error. *Nature Neuroscience* 19, 3-5.
- Conway, K.P., Compton, W., Stinson, F.S., Grant, B.F., 2006. Lifetime comorbidity of DSM-IV mood and anxiety disorders and specific drug use disorders: results from the National Epidemiologic Survey on Alcohol and Related Conditions. *J Clin Psychiatry* 67, 247-257.
- Cook, C.D., Rodefer, J.S., Picker, M.J., 1999. Selective attenuation of the antinociceptive effects of mu opioids by the putative dopamine D-3 agonist 7-OH-DPAT. *Psychopharmacology* 144, 239-247.
- Cools, R., Frank, M.J., Gibbs, S.E., Miyakawa, A., Jagust, W., D'Esposito, M., 2009. Striatal dopamine predicts outcome-specific reversal learning and its sensitivity to dopaminergic drug administration. *J Neurosci* 29, 1538-1543.
- Cools, R., Robinson, O.J., Sahakian, B., 2008. Acute tryptophan depletion in healthy volunteers enhances punishment prediction but does not affect reward prediction. *Neuropsychopharmacology* 33, 1740-2634.
- Cox, Cochran, W.G., 1957. Experimental designs. JSTOR.
- Cox, Reynolds, R.C., Taylor, P.A., 2016. AFNI and clustering: false positive rates redux. *BioRxiv*, 065862.
- Cox, R.W., 1996. AFNI: software for analysis and visualization of functional magnetic resonance neuroimages. *Computers and Biomedical research* 29, 162-173.
- Cox, R.W., Chen, G., Glen, D.R., Reynolds, R.C., Taylor, P.A., 2017. FMRI Clustering in AFNI: False-Positive Rates Redux. *Brain connectivity* 7, 152-171.
- Cox, S.M., Frank, M.J., Larcher, K., Fellows, L.K., Clark, C.A., Leyton, M., Dagher, A., 2015. Striatal D1 and D2 signaling differentially predict learning from positive and negative outcomes. *Neuroimage* 109, 95-101.
- Critchley, H.D., Mathias, C.J., Dolan, R.J., 2002. Fear conditioning in humans: The influence of awareness and autonomic arousal on functional neuroanatomy. *Neuron* 33, 653-663.

- Crockett, M.J., Clark, L., Apergis-Schoute, A.M., Morein-Zamir, S., Robbins, T.W., 2012. Serotonin Modulates the Effects of Pavlovian Aversive Predictions on Response Vigor. *Neuropsychopharmacology* 37, 2244-2252.
- Cuijpers, P., Smit, F., Willemse, G., 2005. Predicting the onset of major depression in subjects with subthreshold depression in primary care: a prospective study. *Acta Psychiatr Scand* 111, 133-138.
- Dale, E., Bang-Andersen, B., Sanchez, C., 2015. Emerging mechanisms and treatments for depression beyond SSRIs and SNRIs. *Biochemical Pharmacology* 95, 81-97.
- Dalgleish, T., Yiend, J., Bramham, J., Teasdale, J.D., Ogilvie, A.D., Malhi, G., Howard, R., 2004. Neuropsychological processing associated with recovery from depression after stereotactic subcaudate tractotomy. *Am J Psychiatry* 161, 1913-1916.
- Dang, L.C., Samanez-Larkin, G.R., Castrellon, J.J., Perkins, S.F., Cowan, R.L., Newhouse, P.A., Zald, D.H., 2017. Spontaneous Eye Blink Rate (EBR) Is Uncorrelated with Dopamine D2 Receptor Availability and Unmodulated by Dopamine Agonism in Healthy Adults. *Eneuro* 4, 11.
- Davey, C.G., Yucel, M., Allen, N.B., 2008. The emergence of depression in adolescence: Development of the prefrontal cortex and the representation of reward. *Neuroscience and Biobehavioral Reviews* 32, 1-19.
- Dean, Z., Horndasch, S., Giannopoulos, P., McCabe, C., 2016. Enhanced neural response to anticipation, effort and consummation of reward and aversion during bupropion treatment. *Psychological Medicine* 46, 2263-2274.
- Delgado, M.R., Li, J., Schiller, D., Phelps, E.A., 2008. The role of the striatum in aversive learning and aversive prediction errors. *Philosophical Transactions of the Royal Society B-Biological Sciences* 363, 3787-3800.
- Der-Avakian, A., Markou, A., 2012. The neurobiology of anhedonia and other reward-related deficits. *Trends in Neurosciences* 35, 68-77.
- Descarries, L., Lemay, B., Doucet, G., Berger, B., 1987. Regional and laminar density of the dopamine innervation in adult rat cerebral cortex. *Neuroscience* 21, 807-824.

- Detre, J.A., Rao, H.Y., Wang, D.J.J., Chen, Y.F., Wang, Z., 2012. Applications of arterial spin labeled MRI in the brain. *Journal of Magnetic Resonance Imaging* 35, 1026-1037.
- Detre, J.A., Wang, J.J., 2002. Technical aspects and utility of fMRI using BOLD and ASL. *Clinical Neurophysiology* 113, 621-634.
- Detre, J.A., Wang, J.J., Wang, Z., Rao, H.Y., 2009. Arterial spin-labeled perfusion MRI in basic and clinical neuroscience. *Current Opinion in Neurology* 22, 348-355.
- Di Chiara, G., North, R.A., 1992. Neurobiology of opiate abuse. *Trends Pharmacol Sci* 13, 185-193.
- Dichter, G.S., Felder, J.N., Petty, C., Bizzell, J., Ernst, M., Smoski, M.J., 2009. The Effects of Psychotherapy on Neural Responses to Rewards in Major Depression. *Biological Psychiatry* 66, 886-897.
- Diekhof, E.K., Kaps, L., Falkai, P., Gruber, O., 2012. The role of the human ventral striatum and the medial orbitofrontal cortex in the representation of reward magnitude - An activation likelihood estimation meta-analysis of neuroimaging studies of passive reward expectancy and outcome processing. *Neuropsychologia* 50, 1252-1266.
- Dimidjian, S., Barrera, M., Jr., Martell, C., Munoz, R.F., Lewinsohn, P.M., 2011. The Origins and Current Status of Behavioral Activation Treatments for Depression. *Annual Review of Clinical Psychology* 7, 1-38.
- Ding, Y., Pereira, F., Hoehne, A., Beaulieu, M.M., Lepage, M., Turecki, G., Jollant, F., 2016. Altered brain processing of decision-making in healthy first-degree biological relatives of suicide completers. *Mol Psychiatry*.
- Disner, S.G., Beevers, C.G., Haigh, E.A.P., Beck, A.T., 2011. Neural mechanisms of the cognitive model of depression. *Nature Reviews Neuroscience* 12, 467-477.
- Dodds, C.M., Muller, U., Clark, L., van Loon, A., Cools, R., Robbins, T.W., 2008. Methylphenidate has differential effects on blood oxygenation level-dependent signal related to cognitive subprocesses of reversal learning. *J Neurosci* 28, 5976-5982.

- Downar, J., Geraci, J., Salomons, T.V., Dunlop, K., Wheeler, S., McAndrews, M.P., Bakker, N., Blumberger, D.M., Daskalakis, Z.J., Kennedy, S.H., Flint, A.J., Giacobbe, P., 2014. Anhedonia and Reward-Circuit Connectivity Distinguish Nonresponders from Responders to Dorsomedial Prefrontal Repetitive Transcranial Magnetic Stimulation in Major Depression. *Biological Psychiatry* 76, 176-185.
- Doyle, O.M., De Simoni, S., Schwarz, A.J., Brittain, C., O'Daly, O.G., Williams, S.C.R., Mehta, M.A., 2013. Quantifying the Attenuation of the Ketamine Pharmacological Magnetic Resonance Imaging Response in Humans: A Validation Using Antipsychotic and Glutamatergic Agents. *Journal of Pharmacology and Experimental Therapeutics* 345, 151-160.
- Dreher, J.C., Schmidt, P.J., Kohn, P., Furman, D., Rubinow, D., Berman, K.F., 2007. Menstrual cycle phase modulates reward-related neural function in women. *Proceedings of the National Academy of Sciences of the United States of America* 104, 2465-2470.
- Dreyer, J.K., Herrik, K.F., Berg, R.W., Hounsgaard, J.D., 2010. Influence of phasic and tonic dopamine release on receptor activation. *J Neurosci* 30, 14273-14283.
- Dubol, M., Trichard, C., Leroy, C., Sandu, A.-L., Rahim, M., Granger, B., Tzavara, E.T., Karila, L., Martinot, J.-L., Artiges, E., 2017a. Dopamine Transporter and Reward Anticipation in a Dimensional Perspective: A Multimodal Brain Imaging Study. *Neuropsychopharmacology* 113-133.
- Duman, R.S., Aghajanian, G.K., 2012. Synaptic Dysfunction in Depression: Potential Therapeutic Targets. *Science* 338, 68-72.
- Dwoskin, L.P., Rauhut, A.S., King-Pospisil, K.A., Bardo, M.T., 2006. Review of the pharmacology and clinical profile of bupropion, an antidepressant and tobacco use cessation agent. *Cns Drug Reviews* 12, 178-207.
- Eisenegger, C., Naef, M., Linssen, A., Clark, L., Gandamaneni, P.K., Muller, U., Robbins, T.W., 2014. Role of Dopamine D2 Receptors in Human Reinforcement Learning. *Neuropsychopharmacology* 39, 2366-2375.

- Ekers, D., Godfrey, C., Gilbody, S., Parrott, S., Richards, D.A., Hammond, D., Hayes, A., 2011a. Cost utility of behavioural activation delivered by the non-specialist. *British Journal of Psychiatry* 199, 510-511.
- Ekers, D., Richards, D., McMillan, D., Bland, J.M., Gilbody, S., 2011b. Behavioural activation delivered by the non-specialist: phase II randomised controlled trial. *British Journal of Psychiatry* 198, 66-72.
- Eklund, A., Nichols, T.E., Knutsson, H., 2016a. Cluster failure: Why fMRI inferences for spatial extent have inflated false-positive rates. *Proceedings of the National Academy of Sciences of the United States of America* 113, 7900-7905.
- Elliott, R., Friston, K.J., Dolan, R.J., 2000. Dissociable neural responses in human reward systems. *Journal of Neuroscience* 20, 6159-6165.
- Elliott, R., Sahakian, B.J., Herrod, J.J., Robbins, T.W., Paykel, E.S., 1997a. Abnormal response to negative feedback in unipolar depression: Evidence for a diagnosis specific impairment. *Journal of Neurology Neurosurgery and Psychiatry* 63, 74-82.
- Elliott, R., Sahakian, B.J., Matthews, K., Bannerjea, A., Rimmer, J., Robbins, T.W., 1997b. Effects of methylphenidate on spatial working memory and planning in healthy young adults. *Psychopharmacology* 131, 196-206.
- Elliott, R., Sahakian, B.J., McKay, A.P., Herrod, J.J., Robbins, T.W., Paykel, E.S., 1996. Neuropsychological impairments in unipolar depression: The influence of perceived failure on subsequent performance. *Psychological Medicine* 26, 975-989.
- Engelmann, J.B., Berns, G.S., Dunlop, B.W., 2017. Hyper-responsivity to losses in the anterior insula during economic choice scales with depression severity. *Psychol Med*, 1-13.
- Eshel, N., Roiser, J.P., 2010. Reward and Punishment Processing in Depression. *Biological Psychiatry* 68, 118-124.
- Evers, E.A., Stiers, P., Ramaekers, J.G., 2017. High reward expectancy during methylphenidate depresses the dopaminergic response to gain and loss. *Social Cognitive and Affective Neuroscience* 12, 311-318.

- Fernandez-Seara, M.A., Aznarez-Sanado, M., Mengual, E., Irigoyen, J., Heukamp, F., Pastor, M.A., 2011. Effects on resting cerebral blood flow and functional connectivity induced by metoclopramide: a perfusion MRI study in healthy volunteers. *British Journal of Pharmacology* 163, 1639-1652.
- Flagel, S.B., Clark, J.J., Robinson, T.E., Mayo, L., Czuj, A., Willuhn, I., Akers, C.A., Clinton, S.M., Phillips, P.E.M., Akil, H., 2011. A selective role for dopamine in stimulus-reward learning. *Nature* 469, 53-63.
- Floyd, T.F., Ratcliffe, S.J., Wang, J., Resch, B., Detre, J.A., 2003. Precision of the CASL-perfusion MRI technique for the measurement of cerebral blood flow in whole brain and vascular territories. *Journal of Magnetic Resonance Imaging* 18, 649-655.
- Forbes, E.E., Dahl, R.E., 2005. Neural systems of positive affect: Relevance to understanding child and adolescent depression? *Development and Psychopathology* 17, 827-850.
- Forbes, E.E., Hariri, A.R., Martin, S.L., Silk, J.S., Moyses, D.L., Fisher, P.M., Brown, S.M., Ryan, N.D., Birmaher, B., Axelson, D.A., Dahl, R.E., 2009. Altered Striatal Activation Predicting Real-World Positive Affect in Adolescent Major Depressive Disorder. *American Journal of Psychiatry* 166, 64-73.
- Forbes, E.E., May, J.C., Siegle, G.J., Ladouceur, C.D., Ryan, N.D., Carter, C.S., Birmaher, B., Axelson, D.A., Dahl, R.E., 2006. Reward-related decision-making in pediatric major depressive disorder: an fMRI study. *Journal of Child Psychology and Psychiatry* 47, 1031-1040.
- Forbes, E.E., Ryan, N.D., Phillips, M.L., Manuck, S.B., Worthman, C.M., Moyses, D.L., Tarr, J.A., Sciarrillo, S.R., Dahl, R.E., 2010. Healthy adolescents' neural response to reward: associations with puberty, positive affect, and depressive symptoms. *J Am Acad Child Adolesc Psychiatry* 49, 162-172.
- Fornaro, M., De Berardis, D., Iasevoli, F., Pistorio, M.L., D'Angelo, E., Mungo, S., Martino, M., Ventriglio, A., Cattaneo, C.I., Favaretto, E., Del Debbio, A., Romano, A., Ciampa, G., Elassy, M., Perugi, G., De Pasquale, C., 2015. Treatment adherence towards prescribed medications in bipolar-II acute depressed patients: Relationship with cyclothymic temperament and

- "therapeutic sensation seeking" in response towards subjective intolerance to pain (vol 151, pg 596, 2013). *Journal of Affective Disorders* 170, 22-22.
- Fornaro, M., De Berardis, D., Koshy, A.S., Perna, G., Valchera, A., Vancampfort, D., Stubbs, B., 2016. Prevalence and clinical features associated with bipolar disorder polypharmacy: a systematic review. *Neuropsychiatric Disease and Treatment* 12, 719-735.
- Fornaro, M., De Berardis, D., Perna, G., Solmi, M., Veronese, N., Orsolini, L., Buonaguro, E.F., Iasevoli, F., Kohler, C.A., Carvalho, A.F., de Bartolomeis, A., 2017. Lurasidone in the Treatment of Bipolar Depression: Systematic Review of Systematic Reviews. *Biomed Research International*.
- Foti, D., Weinberg, A., Dien, J., Hajcak, G., 2011a. Event-related potential activity in the basal ganglia differentiates rewards from nonrewards: temporospatial principal components analysis and source localization of the feedback negativity. *Hum Brain Mapp* 32, 2207-2216.
- Fountoulakis, K.N., Gazouli, M., Kelsoe, J., Akiskal, H., 2015. The pharmacodynamic properties of lurasidone and their role in its antidepressant efficacy in bipolar disorder. *European Neuropsychopharmacology* 25, 335-342.
- Frank, M.J., O'Reilly, R.C., 2006a. A mechanistic account of striatal dopamine function in human cognition: Psychopharmacological studies with cabergoline and haloperidol. *Behavioral Neuroscience* 120, 497-517.
- Franken, I.H.A., Rassin, E., Muris, P., 2007. The assessment of anhedonia in clinical and non-clinical populations: further validation of the Snaith–Hamilton Pleasure Scale (SHAPS). *Journal of Affective Disorders* 99, 83-89.
- Friedman, D.P., Aggleton, J.P., Saunders, R.C., 2002. Comparison of hippocampal, amygdala, and perirhinal projections to the nucleus accumbens: Combined anterograde and retrograde tracing study in the macaque brain. *Journal of Comparative Neurology* 450, 345-365.
- Fu, C.H.Y., Williams, S.C.R., Brammer, M.J., Suckling, J., Kim, J., Cleare, A.J., Walsh, N.D., Mitterschiffthaler, M.T., Andrew, C.M., Pich, E.M., Bullmore, E.T., 2007. Neural responses to happy facial expressions in major depression

- following antidepressant treatment. *American Journal of Psychiatry* 164, 599-607.
- Fu, C.H.Y., Williams, S.C.R., Cleare, A.J., Brammer, M.J., Walsh, N.D., Kim, J., Andrew, C.M., Pich, E.M., Williams, P.M., Reed, L.J., Mitterschiffthaler, M.T., Suckling, J., Bullmore, E.T., 2004. Attenuation of the neural response to sad faces in major depression by antidepressant treatment - A prospective, event-related functional magnetic resonance imaging study. *Archives of General Psychiatry* 61, 877-889.
- Fudge, J.L., Kunishio, K., Walsh, P., Richard, C., Haber, S.N., 2002. Amygdaloid projections to ventromedial striatal subterritories in the primate. *Neuroscience* 110, 257-275.
- Funayama, T., Ikeda, Y., Tateno, A., Takahashi, H., Okubo, Y., Fukayama, H., Suzuki, H., 2014. Modafinil augments brain activation associated with reward anticipation in the nucleus accumbens. *Psychopharmacology* 231, 3217-3228.
- Fusar-Poli, P., Smieskova, R., Kempton, M.J., Ho, B.C., Andreasen, N.C., Borgwardt, S., 2013. Progressive brain changes in schizophrenia related to antipsychotic treatment? A meta-analysis of longitudinal MRI studies. *Neurosci Biobehav Rev* 37, 1680-1691.
- Garrison, J., Erdeniz, B., Done, J., 2013. Prediction error in reinforcement learning: A meta-analysis of neuroimaging studies. *Neuroscience and Biobehavioral Reviews* 37, 1297-1310.
- Gartlehner, G., Hansen, R.A., Morgan, L.C., Thaler, K., Lux, L., Van Noord, M., Mager, U., Thieda, P., Gaynes, B.N., Wilkins, T., Strobelberger, M., Lloyd, S., Reichenpfader, U., Lohr, K.N., 2011. Comparative Benefits and Harms of Second-Generation Antidepressants for Treating Major Depressive Disorder An Updated Meta-analysis. *Ann Intern Med* 155,102-112.
- Gehring, W.J., Willoughby, A.R., 2002. The medial frontal cortex and the rapid processing of monetary gains and losses. *Science* 295, 2279-2282.
- Girgis, R.R., Xu, X.Y., Gil, R.B., Hackett, E., Ojeil, N., Lieberman, J.A., Slifstein, M., Abi-Dargham, A., 2015. Antipsychotic binding to the dopamine-3 receptor in

- humans: A PET study with C-11 -(+)-PHNO. *Schizophrenia Research* 168, 373-376.
- Godlewska, B.R., Browning, M., Norbury, R., Cowen, P.J., Harmer, C.J., 2016. Early changes in emotional processing as a marker of clinical response to SSRI treatment in depression. *Translational Psychiatry* 6.
- Godlewska, B.R., Norbury, R., Selvaraj, S., Cowen, P.J., Harmer, C.J., 2012. Short-term SSRI treatment normalises amygdala hyperactivity in depressed patients. *Psychological Medicine* 42, 2609-2617.
- Goldberg, J.F., Ng-Mak, D., Siu, C., Chuang, C.-C., Rajagopalan, K., Loebel, A., 2017. Remission and recovery associated with lurasidone in the treatment of major depressive disorder with subthreshold hypomanic symptoms (mixed features): post-hoc analysis of a randomized, placebo-controlled study with longer-term extension (vol 22, pg 220, 2017). *CNS Spectrums* 22, 373-373.
- Goldman, R.G., Alexander, G.E., Zemishlany, Z., Mukherjee, S., Sackeim, H., Prohovnik, I., 1996. Acute effects of haloperidol on cerebral cortex blood flow in normal and schizophrenic subjects. *Biological Psychiatry* 40, 604-608.
- Goldstein, R.Z., Cottone, L.A., Jia, Z., Maloney, T., Volkow, N.D., Squires, N.K., 2006. The effect of graded monetary reward on cognitive event-related potentials and behavior in young healthy adults. *International Journal of Psychophysiology* 62, 272-279.
- Gong, L., Yin, Y.Y., He, C.C., Ye, Q., Bai, F., Yuan, Y.G., Zhang, H.S., Lv, L.X., Zhang, H.X., Xie, C.M., Zhang, Z.J., 2017. Disrupted reward circuits is associated with cognitive deficits and depression severity in major depressive disorder. *Journal of Psychiatric Research* 84, 9-17.
- Gonzalez, H.M., Vega, W.A., Williams, D.R., Tarraf, W., West, B.T., Neighbors, H.W., 2010. Depression Care in the United States Too Little for Too Few. *Archives of General Psychiatry* 67, 37-46.
- Goozee, R., Handley, R., Kempton, M.J., Dazzan, P., 2014. A systematic review and meta-analysis of the effects of antipsychotic medications on regional cerebral blood flow (rCBF) in schizophrenia: Association with response to treatment. *Neuroscience and Biobehavioral Reviews* 43, 118-136.

- Gotlib, Hamilton, J.P., Cooney, R.E., Singh, M.K., Henry, M.L., Joormann, J., 2010a. Neural processing of reward and loss in girls at risk for major depression. *Archives of General Psychiatry* 67, 380-387.
- Gotlib, I.H., 1981. Self-Reinforcement And Recall - Differential Deficits In Depressed And Nondepressed Psychiatric-Inpatients. *Journal of Abnormal Psychology* 90, 521-530.
- Gotlib, I.H., Hamilton, J.P., Cooney, R.E., Singh, M.K., Henry, M.L., Joormann, J., 2010b. Neural processing of reward and loss in girls at risk for major depression. *Arch Gen Psychiatry* 67, 380-387.
- Gotlib, I.H., Krasnoperova, E., 1998. Biased information processing as a vulnerability factor for depression. *Behavior Therapy* 29, 603-617.
- Gotlib, I.H., Krasnoperova, E., Yue, D.N., Joormann, J., 2004. Attentional biases for negative interpersonal stimuli in clinical depression. *Journal of Abnormal Psychology* 113, 121-135.
- Gottfried, J.A., O'Doherty, J., Dolan, R.J., 2003. Encoding predictive reward value in human amygdala and orbitofrontal cortex. *Science* 301, 1104-1107.
- Gottlieb, J., Hayhoe, M., Hikosaka, O., Rangel, A., 2014. Attention, Reward, and Information Seeking. *Journal of Neuroscience* 34, 15497-15504.
- Grace, A.A., 1991. Phasic Versus Tonic Dopamine Release And The Modulation Of Dopamine System Responsivity - A Hypothesis For The Etiology Of Schizophrenia. *Neuroscience* 41, 1-24.
- Grace, A.A., 2016. Dysregulation of the dopamine system in the pathophysiology of schizophrenia and depression. *Nature Reviews Neuroscience* 17, 524-534.
- Gradin, V.B., Kumar, P., Waiter, G., Ahearn, T., Stickle, C., Milders, M., Reid, I., Hall, J., Steele, J.D., 2011. Expected value and prediction error abnormalities in depression and schizophrenia. *Brain* 134, 1751-1764.
- Graf, H., Metzger, C.D., Walter, M., Abler, B., 2016. Serotonergic antidepressants decrease hedonic signals but leave learning signals in the nucleus accumbens unaffected. *NeuroReport* 27, 18-22.

- Greenberg, W.M., Citrome, L., 2017. Pharmacokinetics and Pharmacodynamics of Lurasidone Hydrochloride, a Second-Generation Antipsychotic: A Systematic Review of the Published Literature. *Clinical Pharmacokinetics* 56, 493-503.
- Greimel, E., 2011. Sozial-affektive Entwicklung im Jugendalter. Das adoleszente Gehirn. Kohlhammer, Stuttgart, S, 158-172.
- Grimm, S., Ernst, J., Boesiger, P., Schuepbach, D., Hell, D., Boeker, H., Northoff, G., 2009. Increased Self-Focus in Major Depressive Disorder Is Related to Neural Abnormalities in Subcortical-Cortical Midline Structures. *Human Brain Mapping* 30, 2617-2627.
- Grosscup, S.J., Lewinsohn, P.M., 1980. Unpleasant And Pleasant Events, And Mood. *Journal of Clinical Psychology* 36, 252-259.
- Guitart-Masip, M., Chowdhury, R., Sharot, T., Dayan, P., Duzel, E., Dolan, R.J., 2012. Action controls dopaminergic enhancement of reward representations. *Proc Natl Acad Sci U S A* 109, 7511-7516.
- Guyer, A.E., Choate, V.R., Detloff, A., Benson, B., Nelson, E.E., Perez-Edgar, K., Fox, N.A., Pine, D.S., Ernst, M., 2012. Striatal Functional Alteration During Incentive Anticipation in Pediatric Anxiety Disorders. *American Journal of Psychiatry* 169, 205-212.
- Guyer, A.E., McClure, E.B., Adler, A.D., Brotman, M.A., Rich, B.A., Kimes, A.S., Pine, D.S., Ernst, M., Leibenluft, E., 2007. Specificity of facial expression labeling deficits in childhood psychopathology. *J Child Psychol Psychiatry* 48, 863-871.
- Guyer, A.E., Nelson, E.E., Perez-Edgar, K., Hardin, M.G., Roberson-Nay, R., Monk, C.S., Bjork, J.M., Henderson, H.A., Pine, D.S., Fox, N.A., Ernst, M., 2006. Striatal functional alteration in adolescents characterized by early childhood behavioral inhibition. *Journal of Neuroscience* 26, 6399-6405.
- Haber, S.N., Behrens, T.E.J., 2014. The Neural Network Underlying Incentive-Based Learning: Implications for Interpreting Circuit Disruptions in Psychiatric Disorders. *Neuron* 83, 1019-1039.
- Haber, S.N., Knutson, B., 2010. The Reward Circuit: Linking Primate Anatomy and Human Imaging. *Neuropsychopharmacology* 35, 4-26.

- Haber, S.N., Lynd, E., Klein, C., Groenewegen, H.J., 1990. Topographic Organization Of The Ventral Striatal Efferent Projections In The Rhesus-Monkey - An Anterograde Tracing Study. *Journal of Comparative Neurology* 293, 282-298.
- Haber, S.N., McFarland, N.R., 1999. The concept of the ventral striatum in nonhuman primates. Advancing from the Ventral Striatum to the Extended Amygdala: Implications for Neuropsychiatry and Drug Abuse: in Honor of Lennart Heimer 877, 33-48.
- Hagele, C., Schlagenhauf, F., Rapp, M., Sterzer, P., Beck, A., Bermpohl, F., Stoy, M., Strohle, A., Wittchen, H.U., Dolan, R.J., Heinz, A., 2015. Dimensional psychiatry: reward dysfunction and depressive mood across psychiatric disorders. *Psychopharmacology (Berl)* 232, 331-341.
- Hajcak, G., Holroyd, C.B., Moser, J.S., Simons, R.F., 2005. Brain potentials associated with expected and unexpected good and bad outcomes. *Psychophysiology* 42, 161-170.
- Halaris, A.E., Belendiuk, K.T., Freedman, D.X., 1975. Antidepressant Drugs Affect Dopamine Uptake. *Biochemical Pharmacology* 24, 1896-1898.
- Hamid, A.A., Pettibone, J.R., Mabrouk, O.S., Hetrick, V.L., Schmidt, R., Vander Weele, C.M., Kennedy, R.T., Aragona, B.J., Berke, J.D., 2016. Mesolimbic dopamine signals the value of work. *Nature Neuroscience* 19, 117 1546-1726.
- Handley, R., Zelaya, F.O., Reinders, A.A.T.S., Marques, T.R., Mehta, M.A., O'Gorman, R., Alsop, D.C., Taylor, H., Johnston, A., Williams, S., McGuire, P., Pariante, C.M., Kapur, S., Dazzan, P., 2013. Acute effects of single-dose aripiprazole and haloperidol on resting cerebral blood flow (rCBF) in the human brain. *Human Brain Mapping* 34, 272-282.
- Harmer, Bhagwagar, Z., Perrett, D.I., Völlm, B.A., Cowen, P.J., Goodwin, G.M., 2003a. Acute SSRI administration affects the processing of social cues in healthy volunteers. *Neuropsychopharmacology* 28, 148 133-193.
- Harmer, C.J., Cowen, P.J., 2013. 'It's the way that you look at it'-a cognitive neuropsychological account of SSRI action in depression. *Philosophical Transactions of the Royal Society Biological Sciences* 368.

- Harmer, C. J., Duman, R. S., & Cowen, P. J. (2017). How do antidepressants work? New perspectives for refining future treatment approaches. *The Lancet Psychiatry*, 4(5), 409-418.
- Harmer, C.J., Goodwin, G.M., Cowen, P.J., 2009a. Why do antidepressants take so long to work? A cognitive neuropsychological model of antidepressant drug action. *British Journal of Psychiatry* 195, 102-108.
- Harmer, C.J., Hill, S.A., Taylor, M.J., Cowen, P.J., Goodwin, G.M., 2003b. Toward a neuropsychological theory of antidepressant drug action: increase in positive emotional bias after potentiation of norepinephrine activity. *American Journal of Psychiatry* 160, 990-992.
- Harmer, C.J., O'Sullivan, U., Favaron, E., Massey-Chase, R., Ayres, R., Reinecke, A., Goodwin, G.M., Cowen, P.J., 2009c. Effect of Acute Antidepressant Administration on Negative Affective Bias in Depressed Patients. *American Journal of Psychiatry* 166, 1178-1184.
- Harmer, C.J., Shelley, N.C., Cowen, P.J., Goodwin, G.M., 2004. Increased positive versus negative affective perception and memory in healthy volunteers following selective serotonin and norepinephrine reuptake inhibition. *American Journal of Psychiatry* 161, 1256-1263.
- Hasler, G., Drevets, W.C., Manji, H.K., Charney, D.S., 2004. Discovering endophenotypes for major depression. *Neuropsychopharmacology* 29, 1765-1781.
- Hasler, G., Northoff, G., 2011. Discovering imaging endophenotypes for major depression. *Molecular Psychiatry* 16, 604-619.
- Hasson, U., Nusbaum, H.C., Small, S.L., 2009. Task-dependent organization of brain regions active during rest. *Proceedings of the National Academy of Sciences of the United States of America* 106, 10841-10846.
- Hayashi, K., Nakao, K., Nakamura, K., 2015. Appetitive and aversive information coding in the primate dorsal raphe nucleus. *J Neurosci* 35, 6195-6208.
- Helfinstein, S.M., Benson, B., Perez-Edgar, K., Bar-Haim, Y., Detloff, A., Pine, D.S., Fox, N.A., Ernst, M., 2011. Striatal responses to negative monetary outcomes

- differ between temperamentally inhibited and non-inhibited adolescents. *Neuropsychologia* 49, 479-485.
- Heller, A.S., Johnstone, T., Light, S.N., Peterson, M.J., Kolden, G.G., Kalin, N.H., Davidson, R.J., 2013. Relationships Between Changes in Sustained Fronto-Striatal Connectivity and Positive Affect in Major Depression Resulting From Antidepressant Treatment. *American Journal of Psychiatry* 170, 197-206.
- Henriques, J.B., Davidson, R.J., 2000. Decreased responsiveness to reward in depression. *Cognition & Emotion* 14, 711-724.
- Henriques, J.B., Glowacki, J.M., Davidson, R.J., 1994. Reward Fails To Alter Response Bias In Depression. *Journal of Abnormal Psychology* 103, 460-466.
- Henson, R.N.A., Buechel, C., Josephs, O., Friston, K.J., 1999. The slice-timing problem in event-related fMRI. *NeuroImage* 9, 125 1053-8119.
- Herbert, M., Johns, M.W., Doré, C., 1976. Factor analysis of analogue scales measuring subjective feelings before and after sleep. *Psychology and Psychotherapy: Theory, Research and Practice* 49, 373-379.
- Hernaus, D., Mehta, M.A., 2016. Prefrontal cortex dopamine release measured in vivo with positron emission tomography: Implications for the stimulant paradigm. *Neuroimage* 142, 663-667.
- Herzallah, M.M., Moustafa, A.A., Natsheh, J.Y., Abdellatif, S.M., Taha, M.B., Tayem, Y.I., Sehwal, M.A., Amleh, I., Petrides, G., Myers, C.E., 2013. Learning from negative feedback in patients with major depressive disorder is attenuated by SSRI antidepressants. *Front Integr Neurosci* 7.
- Hikida, T., Morita, M., Macpherson, T., 2016. Neural mechanisms of the nucleus accumbens circuit in reward and aversive learning. *Neuroscience Research* 108, 1-5.
- Hikosaka, O., Bromberg-Martin, E., Hong, S., Matsumoto, M., 2008. New insights on the subcortical representation of reward. *Current Opinion in Neurobiology* 18, 203-208.
- Hill, A.B., 1965. Environment And Disease - Association Or Causation. *Proceedings of the Royal Society of Medicine-London* 58, 295-310.

- Hill, A.B., 2015. The environment and disease: association or causation? (Reprinted from *JRSM*, vol 58, 1965). *Journal of the Royal Society of Medicine* 108, 32-37.
- Hodkinson, D.J., Krause, K., Khawaja, N., Renton, T.F., Huggins, J.P., Vennart, W., Thacker, M.A., Mehta, M.A., Zelaya, F.O., Williams, S.C.R., Howard, M.A., 2013. Quantifying the test-retest reliability of cerebral blood flow measurements in a clinical model of on-going post-surgical pain: A study using pseudo-continuous arterial spin labelling. *Neuroimage-Clinical* 3, 301-310.
- Höfler, M., 2005. The Bradford Hill considerations on causality: a counterfactual perspective. *Emerging themes in epidemiology* 2, 11 1742-7622.
- Holmes, A.J., Pizzagalli, D.A., 2007. Task feedback effects on conflict monitoring and executive control: Relationship to subclinical measures of depression. *Emotion* 7, 68-76.
- Holroyd, C.B., Coles, M.G.H., 2002a. The neural basis of human error processing: reinforcement learning, dopamine, and the error-related negativity. *Psychol Rev* 109, 679-709.
- Holroyd, C.B., Larsen, J.T., Cohen, J.D., 2004. Context dependence of the event-related brain potential associated with reward and punishment. *Psychophysiology* 41, 245-253.
- Holroyd, C.B., Umemoto, A., 2016. The research domain criteria framework: The case for anterior cingulate cortex. *Neuroscience and Biobehavioral Reviews* 71, 418-443.
- Holroyd, C.B., Yeung, N., 2012. Motivation of extended behaviors by anterior cingulate cortex. *Trends in Cognitive Sciences* 16, 122-128.
- Holt, R.I.G., Peveler, R.C., 2006. Antipsychotic drugs and diabetes - an application of the Austin Bradford Hill criteria. *Diabetologia* 49, 1467-1476.
- Hopko, D.R., Lejuez, C.W., Ruggiero, K.J., Eifert, G.H., 2003. Contemporary behavioral activation treatments for depression: procedures, principles, and progress. *Clin Psychol Rev* 23, 699-717.
- Horisawa, T., Ishiyama, T., Ono, M., Ishibashi, T., Taiji, M., 2013. Binding of lurasidone, a novel antipsychotic, to rat 5-HT₇ receptor: Analysis by H-3 SB-

- 269970 autoradiography. *Progress in Neuro-Psychopharmacology & Biological Psychiatry* 40, 132-137.
- Huang, M., Horiguchi, M., Felix, A.R., Meltzer, H.Y., 2012. 5-HT_{1A} and 5-HT₇ receptors contribute to lurasidone-induced dopamine efflux. *NeuroReport* 23, 436-440.
- Huneke, N.T.M., Walsh, A.E.L., Brown, R., Browning, M., Harmer, C.J., 2017. No evidence for an acute placebo effect on emotional processing in healthy volunteers. *Journal of Psychopharmacology* 31, 1578-1587.
- Hyman, J.M., Holroyd, C.B., Seamans, J.K., 2017. A Novel Neural Prediction Error Found in Anterior Cingulate Cortex Ensembles. *Neuron* 95, 447-467.
- Iannetti, G.D., Wise, R.G., 2007. BOLD functional MRI in disease and pharmacological studies: room for improvement? *Magnetic Resonance Imaging* 25, 978-988.
- Ichikawa, J., Li, Z., Dai, J., Meltzer, H.Y., 2002. Atypical antipsychotic drugs, quetiapine, iloperidone, and melperone, preferentially increase dopamine and acetylcholine release in rat medial prefrontal cortex: role of 5-HT_{1A} receptor agonism. *Brain Research* 956, 349-357.
- Imhoff, S., Harris, M., Weiser, J., Reynolds, B., 2014. Delay discounting by depressed and non-depressed adolescent smokers and non-smokers. *Drug and Alcohol Dependence* 135, 152-155.
- Inaba, K., Mizuhiki, T., Setogawa, T., Toda, K., Richmond, B.J., Shidara, M., 2013. Neurons in monkey dorsal raphe nucleus code beginning and progress of step-by-step schedule, reward expectation, and amount of reward outcome in the reward schedule task. *J Neurosci* 33, 3477-3491.
- Ishibashi, T., Horisawa, T., Tokuda, K., Ishiyama, T., Ogasa, M., Tagashira, R., Matsumoto, K., Nishikawa, H., Ueda, Y., Toma, S., Oki, H., Tanno, N., Saji, I., Ito, A., Ohno, Y., Nakamura, M., 2010. Pharmacological Profile of Lurasidone, a Novel Antipsychotic Agent with Potent 5-Hydroxytryptamine 7 (5-HT₇) and 5-HT_{1A} Receptor Activity. *Journal of Pharmacology and Experimental Therapeutics* 334, 171-181.

- Ivanov, D., Gardumi, A., Haast, R.A.M., Pfeuffer, J., Poser, B.A., Uludağ, K., 2017. Comparison of 3 T and 7 T ASL techniques for concurrent functional perfusion and BOLD studies. *NeuroImage* 156, 363-376.
- Izquierdo, A., Suda, R.K., Murray, E.A., 2004. Bilateral orbital prefrontal cortex lesions in rhesus monkeys disrupt choices guided by both reward value and reward contingency. *Journal of Neuroscience* 24, 7540-7548.
- Jacobs, E., D'Esposito, M., 2011. Estrogen Shapes Dopamine-Dependent Cognitive Processes: Implications for Women's Health. *Journal of Neuroscience* 31, 5286-5293.
- Jacobson, N.S., Martell, C.R., Dimidjian, S., 2001. Behavioral Activation Treatment for Depression: Returning to Contextual Roots. *Clinical Psychology: Science and Practice* 8, 255-270.
- Jaeschke, R.R., Sowa-Kucma, M., Panczyszyn-Trzewik, P., Misztak, P., Styczen, K., Datka, W., 2016. Lurasidone: The 2016 update on the pharmacology, efficacy and safety profile. *Pharmacological Reports* 68, 748-755.
- Jahng, G.H., Song, E.M., Zhu, X.P., Matson, G.B., Weiner, M.W., Schuff, N., 2005. Human brain: Reliability and reproducibility of pulsed arterial spin-labeling perfusion MR imaging. *Radiology* 234, 909-916.
- Jenkins, R., Bebbington, P., Brugha, T., Farrell, M., Gill, B., Lewis, G., Meltzer, H., Petticrew, M., 1997. The National Psychiatric Morbidity Surveys of Great Britain - strategy and methods. *Psychological Medicine* 27, 765-774.
- Jensen, J., Smith, A.J., Willeit, M., Crawley, A.P., Mikulis, D.J., Vitcu, I., Kapur, S., 2007. Separate brain regions code for salience vs. valence during reward prediction in humans. *Human Brain Mapping* 28, 294-302.
- Jocham, G., Klein, T.A., Ullsperger, M., 2011. Dopamine-Mediated Reinforcement Learning Signals in the Striatum and Ventromedial Prefrontal Cortex Underlie Value-Based Choices. *Journal of Neuroscience* 31, 1606-1613.
- Jocham, G., Klein, T.A., Ullsperger, M., 2014. Differential Modulation of Reinforcement Learning by D2 Dopamine and NMDA Glutamate Receptor Antagonism. *Journal of Neuroscience* 34, 13151-13162.

- Johnston, B.A., Tolomeo, S., Gradin, V., Christmas, D., Matthews, K., Steele, J.D., 2015. Failure of hippocampal deactivation during loss events in treatment-resistant depression. *Brain* 138, 2766-2776.
- Jollant, F., Richard-Devantoy, S., Ding, Y., Turecki, G., Bechara, A., Near, J., 2016. Prefrontal inositol levels and implicit decision-making in healthy individuals and depressed patients. *Eur Neuropsychopharmacol* 26, 1255-1263.
- Jongkees, B.J., Colzato, L.S., 2016. Spontaneous eye blink rate as predictor of dopamine-related cognitive function-A review. *Neuroscience and Biobehavioral Reviews* 71, 58-82.
- Juckel, G., 2016. Inhibition of the reward system by antipsychotic treatment. *Dialogues Clin Neurosci* 18, 109-114.
- Juckel, G., Schlagenhauf, F., Koslowski, M., Filonov, D., Wuestenberg, T., Villringer, A., Knutson, B., Kienast, T., Gallinat, J., Wrase, J., Heinz, A., 2006. Dysfunction of ventral striatal reward prediction in schizophrenic patients treated with typical, not atypical, neuroleptics. *Psychopharmacology* 187, 222-228.
- Karpova, N.N., Pickenhagen, A., Lindholm, J., Tiraboschi, E., Kuleskaya, N., Agustsdottir, A., Antila, H., Popova, D., Akamine, Y., Sullivan, R., Hen, R., Drew, L.J., Castren, E., 2011. Fear Erasure in Mice Requires Synergy Between Antidepressant Drugs and Extinction Training. *Science* 334, 1731-1734.
- Kendler, K.S., 2016. The Phenomenology of Major Depression and the Representativeness and Nature of DSM Criteria. *American Journal of Psychiatry* 173, 771-780.
- Kendler, K.S., 2017. The genealogy of major depression: symptoms and signs of melancholia from 1880 to 1900. *Molecular Psychiatry* 22, 1539-1553.
- Keren, H., O'Callaghan, G., Vidal-Ribas, P., Buzzell, G., Brotman, M., E., L., Pan, P., Meffert, L., Kaisera, A., Wolke, S., Pine, D., Stringaris, A., 2018. Reward processing in depression: a conceptual and meta-analytic review across electrophysiological and fMRI studies. *American Journal of Psychiatry*.

- Kerestes, R., Davey, C.G., Stephanou, K., Whittle, S., Harrison, B.J., 2014. Functional brain imaging studies of youth depression: A systematic review. *Neuroimage-Clinical* 4, 209-231.
- Kessler, R.C., Demler, O., Frank, R.G., Olfson, M., Pincus, H.A., Walters, E.E., Wang, P., Wells, K.B., Zaslavsky, A.M., 2005. Prevalence and treatment of mental disorders, 1990 to 2003. *New England Journal of Medicine* 352, 2515-2523.
- Klein, D.C., Fencilmorse, E., Seligman, M.E.P., 1976. Learned Helplessness, Depression, And Attribution Of Failure. *Journal of Personality and Social Psychology* 33, 508-516.
- Klein, D.N., Glenn, C.R., Kosty, D.B., Seeley, J.R., Rohde, P., Lewinsohn, P.M., 2013. Predictors of first lifetime onset of major depressive disorder in young adulthood. *J Abnorm Psychol* 122, 1-6.
- Knutson, B., Adams, C.M., Fong, G.W., Hommer, D., 2001. Anticipation of increasing monetary reward selectively recruits nucleus accumbens. *J Neurosci* 21, 1-5.
- Knutson, B., Bhanji, J.P., Cooney, R.E., Atlas, L.Y., Gotlib, I.H., 2008. Neural responses to monetary incentives in major depression. *Biological Psychiatry* 63, 686-692.
- Knutson, B., Fong, G.W., Bennett, S.M., Adams, C.M., Homme, D., 2003. A region of mesial prefrontal cortex tracks monetarily rewarding outcomes: characterization with rapid event-related fMRI. *NeuroImage* 18, 263-272.
- Knutson, B., Taylor, J., Kaufman, M., Peterson, R., Glover, G., 2005. Distributed neural representation of expected value. *Journal of Neuroscience* 25, 4806-4812.
- Knutson, B., Westdorp, A., Kaiser, E., Hommer, D., 2000. FMRI visualization of brain activity during a monetary incentive delay task. *Neuroimage* 12, 20-27.
- Koch, S., Perry, K.W., Bymaster, F.P., 2004. Brain region and dose effects of an olanzapine/fluoxetine combination on extracellular monoamine concentrations in the rat. *Neuropharmacology* 46, 232-242.

- Korte, S.M., Prins, J., Krajnc, A.M., Hendriksen, H., Oosting, R.S., Westphal, K.G., Korte-Bouws, G.A.H., Olivier, B., 2015. The many different faces of major depression: It is time for personalized medicine. *European Journal of Pharmacology* 753, 88-104.
- Kraemer, H.C., Wilson, G.T., Fairburn, C.G., Agras, W.S., 2002. Mediators and moderators of treatment effects in randomized clinical trials. *Archives of General Psychiatry* 59, 877-883.
- Krefetz, D.G., Steer, R.A., Gulab, N.A., Beck, A.T., 2002. Convergent validity of the Beck Depression Inventory-II with the Reynolds Adolescent Depression Scale in psychiatric inpatients. *Journal of Personality Assessment* 78, 451-460.
- Kremer, E.F., 1978. Rescorla-Wagner Model - Losses In Associative Strength In Compound Conditioned Stimuli. *Journal of Experimental Psychology-Animal Behavior Processes* 4, 22-36.
- Kriegeskorte, N., Simmons, W.K., Bellgowan, P.S., Baker, C.I., 2009. Circular analysis in systems neuroscience: the dangers of double dipping. *Nature Neuroscience* 12, 535-540.
- Krystal, J.H., State, M.W., 2014. Psychiatric Disorders: Diagnosis to Therapy. *Cell* 157, 201-214.
- Kujawa, A., Burkhouse, K.L., 2017. Vulnerability to Depression in Youth: Advances from Affective Neuroscience. *Biological psychiatry. Cognitive neuroscience and neuroimaging* 2, 28-37.
- Kumar, G., Steer, R.A., Teitelman, K.B., Villacis, L., 2002. Effectiveness of Beck Depression Inventory-II subscales in screening for major depressive disorders in adolescent psychiatric inpatients. *Assessment* 9, 164-170.
- Kumar, P., Waiter, G., Ahearn, T., Milders, M., Reid, I., Steele, J.D., 2008. Abnormal temporal difference reward-learning signals in major depression. *Brain* 131, 2084-2093.
- la Fougere, C., Meisenzahl, E., Schmitt, G., Stauss, J., Frodl, T., Tatsch, K., Hahn, K., Moller, H.J., Dresel, S., 2005. D-2 receptor occupancy during high- and low-dose therapy with the atypical antipsychotic amisulpride: A I-123-Iodobenzamide SPECT study. *Journal of Nuclear Medicine* 46, 1028-1033.

- Lahti, Holcomb, H.H., Weiler, M.A., Medoff, D.R., Tamminga, C.A., 2003. Functional effects of antipsychotic drugs: comparing clozapine with haloperidol. *Biological Psychiatry* 53, 601-608.
- Lahti, Weiler, M.A., Medoff, D.R., Tamminga, C.A., Holcomb, H.H., 2005. Functional effects of single dose first- and second-generation antipsychotic administration in subjects with schizophrenia. *Psychiatry Research-Neuroimaging* 139, 19-30.
- Laidi, C., Houenou, J., 2016. Brain functional effects of psychopharmacological treatments in bipolar disorder. *European Neuropsychopharmacology* 26, 1695-1740.
- Lally, N., Nugent, A.C., Luckenbaugh, D.A., Ameli, R., Roiser, J.P., Zarate, C.A., 2014. Anti-anhedonic effect of ketamine and its neural correlates in treatment-resistant bipolar depression. *Translational Psychiatry* 4.
- Lally, N., Nugent, A.C., Luckenbaugh, D.A., Niciu, M.J., Roiser, J.P., Zarate, C.A., Jr., 2015. Neural correlates of change in major depressive disorder anhedonia following open-label ketamine. *J Psychopharmacol* 29, 596-607.
- Lamers, F., Milaneschi, Y., de Jonge, P., Giltay, E.J., Penninx, B., 2017. Metabolic and inflammatory markers: associations with individual depressive symptoms. *Psychol Med*, 1-11.
- Landes, I., Bakos, S., Kohls, G., Bartling, J., Schulte-Koerne, G., Greimel, E., 2018. Altered neural processing of reward and punishment in adolescents with Major Depressive Disorder. *Journal of affective disorders* 165-327.
- Lasa, L., Ayuso-Mateos, J.L., Vazquez-Barquero, J.L., Diez-Manrique, F.J., Dowrick, C.F., 2000. The use of the Beck Depression Inventory to screen for depression in the general population: a preliminary analysis. *Journal of Affective Disorders* 57, 261-265.
- Lataster, J., van Os, J., de Haan, L., Thewissen, V., Bak, M., Lataster, T., Lardinois, M., Delespaul, P., Myin-Germeys, I., 2011. Emotional Experience and Estimates of D-2 Receptor Occupancy in Psychotic Patients Treated With Haloperidol, Risperidone, or Olanzapine: An Experience Sampling Study. *Journal of Clinical Psychiatry* 72, 1397-1404.

- Lauritzen, M., 2001. Relationship of spikes, synaptic activity, and local changes of cerebral blood flow. *Journal of Cerebral Blood Flow and Metabolism* 21, 1367-1383.
- Lempert, K.M., Pizzagalli, D.A., 2010. Delay discounting and future-directed thinking in anhedonic individuals. *J Behav Ther Exp Psychiatry* 41, 258-264.
- Leventhal, A.M., Chasson, G.S., Tapia, E., Miller, E.K., Pettit, J.W., 2006. Measuring hedonic capacity in depression: a psychometric analysis of three anhedonia scales. *Journal of Clinical Psychology* 62, 1545-1558.
- Lewinsohn, P.M., Amenson, C.S., 1978. Some Relations Between Pleasant And Unpleasant Mood-Related Events And Depression. *Journal of Abnormal Psychology* 87, 644-654.
- Lewinsohn, P.M., Graf, M., 1973. Pleasant Activities And Depression. *Journal of Consulting and Clinical Psychology* 41, 261-268.
- Lewinsohn, P.M., Libet, J., 1972. Pleasant Events, Activity Schedules, And Depressions. *Journal of Abnormal Psychology* 79, 291-301.
- Lewinsohn, P.M., Lobitz, W.C., Wilson, S., 1973. Sensitivity Of Depressed Individuals To Aversive Stimuli. *Journal of Abnormal Psychology* 81, 259-263.
- Lewinsohn, P.M., Mermelstein, R.M., Alexander, C., Macphillamy, D.J., 1985. The Unpleasant Events Schedule - A Scale For The Measurement Of Aversive Events. *Journal of Clinical Psychology* 41, 483-498.
- Lewinsohn, P.M., Solomon, A., Seeley, J.R., Zeiss, A., 2000. Clinical implications of "subthreshold" depressive symptoms. *Journal of Abnormal Psychology* 109, 345-351.
- Lewinsohn, P.M., Talkington, J., 1979. Studies on the measurement of unpleasant events and relations with depression. *Applied Psychological Measurement* 3, 83-101.
- Leyton, M., aan het Rot, M., Booij, L., Baker, G.B., Young, S.N., Benkelfat, C., 2007. Mood-elevating effects of d-amphetamine and incentive salience: the effect of acute dopamine precursor depletion. *J Psychiatry Neurosci* 32, 129-136.

- Leyton, M., Young, S.N., Pihl, R.O., Etezadi, S., Lauze, C., Blier, P., Baker, G.B., Benkelfat, C., 2000. Effects on mood of acute phenylalanine/tyrosine depletion in healthy women. *Neuropsychopharmacology* 22, 52-63.
- Li, Y., Zhong, W., Wang, D., Feng, Q., Liu, Z., Zhou, J., Jia, C., Hu, F., Zeng, J., Guo, Q., Fu, L., Luo, M., 2016. Serotonin neurons in the dorsal raphe nucleus encode reward signals. *Nat Commun* 7, 10503.
- Linke, J., Wessa, M., 2017. Mental Imagery Training Increases Wanting of Rewards and Reward Sensitivity and Reduces Depressive Symptoms. *Behavior Therapy* 48, 695-706.
- Liu, X., Hairston, J., Schrier, M., Fan, J., 2011. Common and distinct networks underlying reward valence and processing stages: A meta-analysis of functional neuroimaging studies. *Neuroscience and Biobehavioral Reviews* 35, 1219-1236.
- Liu, Z., Zhou, J., Li, Y., Hu, F., Lu, Y., Ma, M., Feng, Q., Zhang, J.E., Wang, D., Zeng, J., Bao, J., Kim, J.Y., Chen, Z.F., El Mestikawy, S., Luo, M., 2014. Dorsal raphe neurons signal reward through 5-HT and glutamate. *Neuron* 81, 1360-1374.
- Ljungberg, T., Apicella, P., Schultz, W., 1992. Responses Of Monkey Dopamine Neurons During Learning Of Behavioral Reactions. *Journal of Neurophysiology* 67, 145-163.
- Loebel, A., Citrome, L., 2015. Lurasidone: a novel antipsychotic agent for the treatment of schizophrenia and bipolar depression. *BJPsych bulletin* 39, 237-241.
- Loebel, A., Cucchiaro, J., Silva, R., Kroger, H., Hsu, J., Sarma, K., Sachs, G., 2014a. Lurasidone Monotherapy in the Treatment of Bipolar I Depression: A Randomized, Double-Blind, Placebo-Controlled Study. *American Journal of Psychiatry* 171, 160-168.
- Loebel, A., Cucchiaro, J., Silva, R., Kroger, H., Hsu, J., Sarma, K., Sachs, G., 2014b. Lurasidone monotherapy in the treatment of bipolar I depression: a randomized, double-blind, placebo-controlled study. *Am J Psychiatry* 171, 160-168.

- Loebel, A., Cucchiaro, J., Silva, R., Kroger, H., Sarma, K., Xu, J., Calabrese, J.R., 2014c. Lurasidone as Adjunctive Therapy With Lithium or Valproate for the Treatment of Bipolar I Depression: A Randomized, Double-Blind, Placebo-Controlled Study. *American Journal of Psychiatry* 171, 169-177.
- Loebel, A.D., Siu, C.O., Cucchiaro, J.B., Pikalov, A.A., Harvey, P.D., 2014d. Daytime sleepiness associated with lurasidone and quetiapine XR: results from a randomized double-blind, placebo-controlled trial in patients with schizophrenia. *CNS Spectrums* 19, 197-205.
- Logothetis, N.K., Pauls, J., Augath, M., Trinath, T., Oeltermann, A., 2001. Neurophysiological investigation of the basis of the fMRI signal. *Nature* 412, 150-157.
- Logothetis, N.K., Pfeuffer, J., 2004. On the nature of the BOLD fMRI contrast mechanism. *Magnetic Resonance Imaging* 22, 1517-1531.
- Logothetis, N.K., Wandell, B.A., 2004. Interpreting the BOLD signal. *Annual Review of Physiology* 66, 735-769.
- Luck, S.J., Kappenman, E.S., 2011. *The Oxford handbook of event-related potential components*. Oxford university press.
- Luking, Pagliaccio, Luby, Barch, 2016a. Depression risk predicts blunted neural responses to gains and enhanced responses to losses in healthy children. *Journal of the American Academy of Child & Adolescent Psychiatry* 55, 328-337.
- Lutz, K., Widmer, M., 2014. What can the monetary incentive delay task tell us about the neural processing of reward and punishment. *Neuroscience and Neuroeconomics* 3, 33-35.
- Luu, P., Tucker, D.M., Derryberry, D., Reed, M., Poulsen, C., 2003. Electrophysiological responses to errors and feedback in the process of action regulation. *Psychol Sci* 14, 47-53.
- Ma, Y., 2015. Neuropsychological mechanism underlying antidepressant effect: a systematic meta-analysis. *Molecular Psychiatry* 20, 311-319.
- Macoveanu, J., 2014. Serotonergic modulation of reward and punishment: Evidence from pharmacological fMRI studies. *Brain Research* 1556, 19-27.

- Macoveanu, J., Fisher, P.M., Haahr, M.E., Frokjaer, V.G., Knudsen, G.M., Siebner, H.R., 2014. Effects of selective serotonin reuptake inhibition on neural activity related to risky decisions and monetary rewards in healthy males. *NeuroImage* 99, 434-442.
- Macoveanu, J., Rowe, J.B., Hornboll, B., Elliott, R., Paulson, O.B., Knudsen, G.M., Siebner, H.R., 2013. Playing it safe but losing anyway-Serotonergic signaling of negative outcomes in dorsomedial prefrontal cortex in the context of risk-aversion. *European Neuropsychopharmacology* 23, 919-930.
- Macphillamy, D.J., Lewinsohn, P.M., 1974. Depression As A Function Of Levels Of Desired And Obtained Pleasure. *Journal of Abnormal Psychology* 83, 651-657.
- MacQueen, G., Santaguida, P., Keshavarz, H., Jaworska, N., Levine, M., Beyene, J., Raina, P., 2017. Systematic Review of Clinical Practice Guidelines for Failed Antidepressant Treatment Response in Major Depressive Disorder, Dysthymia, and Subthreshold Depression in Adults. *Canadian Journal of Psychiatry-Revue Canadienne De Psychiatrie* 62, 11-23.
- Marquand, A.F., De Simoni, S., O'Daly, O.G., Williams, S.C.R., Mourao-Miranda, J., Mehta, M.A., 2011. Pattern Classification of Working Memory Networks Reveals Differential Effects of Methylphenidate, Atomoxetine, and Placebo in Healthy Volunteers. *Neuropsychopharmacology* 36, 1237-1247.
- Martin-Soelch, C., 2009. Is depression associated with dysfunction of the central reward system? *Biochemical Society Transactions* 37, 313-317.
- Martinotti, G., Sepede, G., Gambi, F., Di Iorio, G., De Berardis, D., Di Nicola, M., Onofrj, M., Janiri, L., Di Giannantonio, M., 2012. Agomelatine versus venlafaxine XR in the treatment of anhedonia in major depressive disorder: a pilot study. *Journal of Clinical Psychopharmacology* 32, 487-491.
- Martins, D., Mehta, M.A., Prata, D., 2017. The "highs and lows" of the human brain on dopaminergics: Evidence from neuropharmacology. *Neuroscience and Biobehavioral Reviews* 80, 351-371.
- Marton, P., Churchard, M., Kutcher, S., Korenblum, M., 1991. Diagnostic Utility Of The Beck Depression Inventory With Adolescent Psychiatric Outpatients And

- Inpatients. *Canadian Journal of Psychiatry-Revue Canadienne De Psychiatrie* 36, 428-431.
- Marutani, T., Yahata, N., Ikeda, Y., Ito, T., Yamamoto, M., Matsuura, M., Matsushima, E., Okubo, Y., Suzuki, H., Matsuda, T., 2011. Functional magnetic resonance imaging study on the effects of acute single administration of paroxetine on motivation-related brain activity. *Psychiatry and Clinical Neurosciences* 65, 191-198.
- Mato Abad, V., Garcia-Polo, P., O'Daly, O., Antonio Hernandez-Tamames, J., Zelaya, F., 2016. ASAP (Automatic Software for ASL Processing): A toolbox for processing Arterial Spin Labeling images. *Magnetic Resonance Imaging* 34, 334-344.
- Matthews, P.M., Hampshire, A., 2016. Clinical Concepts Emerging from fMRI Functional Connectomics. *Neuron* 91, 511-528.
- Mayo, L.M., Fraser, D., Childs, E., Momenan, R., Hommer, D.W., de Wit, H., Heilig, M., 2013. Conditioned preference to a methamphetamine-associated contextual cue in humans. *Neuropsychopharmacology* 38, 921-929.
- McCabe, C., Cowen, P.J., Harmer, C.J., 2009. Neural representation of reward in recovered depressed patients. *Psychopharmacology* 205, 667-677.
- McCabe, C., Huber, A., Harmer, C.J., Cowen, P.J., 2011. The D2 antagonist sulpiride modulates the neural processing of both rewarding and aversive stimuli in healthy volunteers. *Psychopharmacology (Berl)* 217, 271-278.
- McCabe, C., Mishor, Z., Cowen, P.J., Harmer, C.J., 2010. Diminished Neural Processing of Aversive and Rewarding Stimuli During Selective Serotonin Reuptake Inhibitor Treatment. *Biological Psychiatry* 67, 439-445.
- McCabe, C., Woffindale, C., Harmer, C.J., Cowen, P.J., 2012. Neural Processing of Reward and Punishment in Young People at Increased Familial Risk of Depression. *Biological Psychiatry* 72, 588-594.
- McClure, S.M., Berns, G.S., Montague, P.R., 2003. Temporal prediction errors in a passive learning task activate human striatum. *Neuron* 38, 339-346.

- McCullough, L.D., Salamone, J.D., 1992. Involvement Of Nucleus-Accumbens Dopamine In The Motor-Activity Induced By Periodic Food Presentation - A Microdialysis And Behavioral-Study. *Brain Research* 592, 29-36.
- McEwen, B.S., Bowles, N.P., Gray, J.D., Hill, M.N., Hunter, R.G., Karatsoreos, I.N., Nasca, C., 2015. Mechanisms of stress in the brain. *Nature Neuroscience* 18, 1353-1363.
- McEwen, B.S., Morrison, J.H., 2013. The Brain on Stress: Vulnerability and Plasticity of the Prefrontal Cortex over the Life Course. *Neuron* 79, 16-29.
- McFarland, B.R., Klein, D.N., 2009. Emotional Reactivity In Depression: Diminished Responsiveness To Anticipated Reward But Not To Anticipated Punishment Or To Nonreward Or Avoidance. *Depression and Anxiety* 26, 117-122.
- McIntyre, R.S., Cha, D.S., Kim, R.D., Mansur, R.B., 2013. A review of FDA-approved treatment options in bipolar depression. *CNS Spectrums* 18 Suppl 1, 4-21.
- McIntyre, R.S., Cucchiaro, J., Pikalov, A., Kroger, H., Loebel, A., 2015. Lurasidone in the Treatment of Bipolar Depression With Mixed (Subsyndromal Hypomanic) Features: Post Hoc Analysis of a Randomized Placebo-Controlled Trial. *Journal of Clinical Psychiatry* 76, 398-405.
- McLean, A., Rubinsztein, J.S., Robbins, T.W., Sahakian, B.J., 2004b. The effects of tyrosine depletion in normal healthy volunteers: implications for unipolar depression. *Psychopharmacology* 171, 286-297.
- McMakin, D.L., Olino, T.M., Porta, G., Dietz, L.J., Emslie, G., Clarke, G., Wagner, K.D., Asarnow, J.R., Ryan, N.D., Birmaher, B., Shamseddeen, W., Mayes, T., Kennard, B., Spirito, A., Keller, M., Lynch, F.L., Dickerson, J.F., Brent, D.A., 2012. Anhedonia Predicts Poorer Recovery Among Youth With Selective Serotonin Reuptake Inhibitor Treatment-Resistant Depression. *Journal of the American Academy of Child and Adolescent Psychiatry* 51, 404-411.
- McRobbie, D.W., Moore, E.A., Graves, M.J., Prince, M.R., 2006. *MRI from picture to proton*. Cambridge University Press, Cambridge.
- Mehta, M.A., McGowan, S.W., Lawrence, A.D., Aitken, M.R.F., Montgomery, A.J., Grasby, P.M., 2003. Systemic sulpiride modulates striatal blood flow:

- relationships to spatial working memory and planning. *NeuroImage* 20, 1982-1994.
- Melega, W.P., Williams, A.E., Schmitz, D.A., DiStefano, E.W., Cho, A.K., 1995. Pharmacokinetic and pharmacodynamic analysis of the actions of D-amphetamine and D-methamphetamine on the dopamine terminal. *J Pharmacol Exp Ther* 274, 90-96.
- Menon, M., Jensen, J., Vitcu, I., Graff-Guerrero, A., Crawley, A., Smith, M.A., Kapur, S., 2007a. Temporal difference modeling of the blood-oxygen level dependent response during aversive conditioning in humans: Effects of dopaminergic modulation. *Biological Psychiatry* 62, 765-772.
- Michels, L., Scherpiet, S., Stampfli, P., Herwig, U., Bruhl, A.B., 2016. Baseline Perfusion Alterations Due to Acute Application of Quetiapine and Pramipexole in Healthy Adults. *International Journal of Neuropsychopharmacology* 19.
- Miller, G.A., Chapman, J.P., 2001. Misunderstanding analysis of covariance. *Journal of Abnormal Psychology* 110, 40-48.
- Moniz, M., De Jesus, S.N., Gonçalves, E., Pacheco, A., Viseu, J., 2016. Decision-making in adult unipolar depressed patients and healthy subjects: Significant differences in Net Score and in non-traditional alternative measures. *Neuropsychological Trends* 19, 7-15.
- Montague, P.R., McClure, S.M., Baldwin, P.R., Phillips, P.E.M., Budygin, E.A., Stuber, G.D., Kilpatrick, M.R., Wightman, R.M., 2004. Dynamic gain control of dopamine delivery in freely moving animals. *Journal of Neuroscience* 24, 1754-1759.
- Morgan, J.K., Olino, T.M., McMakin, D.L., Ryan, N.D., Forbes, E.E., 2013. Neural response to reward as a predictor of increases in depressive symptoms in adolescence. *Neurobiology of disease* 52, 66-74.
- Morgan, J.K., Shaw, D.S., Olino, T.M., Musselman, S.C., Kurapati, N.T., Forbes, E.E., 2016. History of Depression and Frontostriatal Connectivity During Reward Processing in Late Adolescent Boys. *J Clin Child Adolesc Psychol* 45, 59-68.

- Mori, A., Okamoto, Y., Okada, G., Takagaki, K., Jinnin, R., Takamura, M., Kobayakawa, M., Yamawaki, S., 2016a. Behavioral activation can normalize neural hypoactivation in subthreshold depression during a monetary incentive delay task. *J Affect Disord* 189, 254-262.
- Morita, K., Morishima, M., Sakai, K., Kawaguchi, Y., 2012. Reinforcement learning: computing the temporal difference of values via distinct corticostriatal pathways. *Trends in Neurosciences* 35, 457-467.
- Morris, S.E., Cuthbert, B.N., 2012. Research Domain Criteria: cognitive systems, neural circuits, and dimensions of behavior. *Dialogues Clin Neurosci* 14, 29-37.
- Murphy, F.C., Michael, A., Robbins, T.W., Sahakian, B.J., 2003. Neuropsychological impairment in patients with major depressive disorder: the effects of feedback on task performance. *Psychological Medicine* 33, 455-467.
- Murphy, S.E., Norbury, R., O'Sullivan, U., Cowen, P.J., Harmer, C.J., 2009. Effect of a single dose of citalopram on amygdala response to emotional faces. *British Journal of Psychiatry* 194, 535-540.
- Must, A., Szabo, Z., Bodi, N., Szasz, A., Janka, Z., Keri, S., 2006. Sensitivity to reward and punishment and the prefrontal cortex in major depression. *J Affect Disord* 90, 209-215.
- Nakonezny, P.A., Carmody, T.J., Morris, D.W., Kurian, B.T., Trivedi, M.H., 2010. Psychometric evaluation of the Snaith–Hamilton Pleasure Scale (SHAPS) in adult outpatients with major depressive disorder. *International Clinical Psychopharmacology* 25, 328.
- Nakonezny, P.A., Morris, D.W., Greer, T.L., Byerly, M.J., Carmody, T.J., Grannemann, B.D., Bernstein, I.H., Trivedi, M.H., 2015. Evaluation of anhedonia with the Snaith–Hamilton Pleasure Scale (SHAPS) in adult outpatients with major depressive disorder. *Journal of Psychiatric Research* 65, 124-130.
- Nelson, Suppes, T., Tsai, J., Mao, Y., Pikalov, A., Loebel, A., 2015. Lurasidone for Major Depressive Disorder with Mixed Features: Effect of Baseline

- Depression Severity on Clinical Outcome. *Neuropsychopharmacology* 40, 330-341.
- Nelson, Willison, J., 1991. The revised national adult reading test—test manual. Windsor, UK: NFER-Nelson 991.
- Nelson, B.D., Perlman, G., Klein, D.N., Kotov, R., Hajcak, G., 2016. Blunted Neural Response to Rewards as a Prospective Predictor of the Development of Depression in Adolescent Girls. *Am J Psychiatry* 173, 1223-1230.
- Nestler, E.J., 1998. Antidepressant treatments in the 21st century. *Biological Psychiatry* 44, 526-533.
- Nestler, E.J., Carlezon, W.A., 2006. The mesolimbic dopamine reward circuit in depression. *Biological Psychiatry* 59, 1151-1159.
- Nierenberg, A., Tsai, J., Mao, Y., Pikalov, A., Suppes, T., Loebel, A., 2015. Efficacy of Lurasidone in Major Depression with Mixed Features: Pattern of Improvement in Depressive and Manic Symptoms. *Neuropsychopharmacology* 40, 141-150.
- Noble, E.P., Blum, K., Ritchie, T., Montgomery, A., Sheridan, P.J., 1991. Allelic association of the D2 dopamine receptor gene with receptor-binding characteristics in alcoholism. *Arch Gen Psychiatry* 48, 648-654.
- Norbury, R., MacKay, C.E., Cowen, P.J., Goodwin, G.M., Harmer, C.J., 2007. Short-term antidepressant treatment and facial processing - Functional magnetic resonance imaging study. *British Journal of Psychiatry* 190, 531-532.
- Nosworthy, J.H., Ebers, G.C., Vandervoort, M.K., Farquhar, R.E., Yetisir, E., Roberts, R., 2001. The impact of blinding on the results of a randomized, placebo-controlled multiple sclerosis clinical trial. *Neurology* 57, 31-35.
- Novak, K.D., Foti, D., 2015. Teasing apart the anticipatory and consummatory processing of monetary incentives: An event-related potential study of reward dynamics. *Psychophysiology* 52, 1470-1482.
- Nutt, D., Demyttenaere, K., Janka, Z., Aarre, T., Bourin, M., Canonico, P.L., Carrasco, J.L., Stahl, S., 2007. The other face of depression, reduced positive affect: the role of catecholamines in causation and cure. *Journal of Psychopharmacology* 21, 461-471.

- O'Daly, O.G., Joyce, D., Tracy, D.K., Azim, A., Stephan, K.E., Murray, R.M., Shergill, S.S., 2014. Amphetamine sensitization alters reward processing in the human striatum and amygdala. *PLoS One* 9, 939-955.
- O'Doherty, J., Dayan, P., Schultz, J., Deichmann, R., Friston, K.J., Dolan, R.J., 2004. Dissociable roles of ventral and dorsal striatum in instrumental conditioning. *Science* 304, 452-454.
- O'Doherty, J.P., 2004. Reward representations and reward-related learning in the human brain: insights from neuroimaging. *Current Opinion in Neurobiology* 14, 769-776.
- O'Doherty, J.P., Dayan, P., Friston, K.J., Critchley, H., Dolan, R.J., 2003. Temporal difference models and reward-related learning in the human brain. *Neuron* 38, 329-337.
- Odum, A.L., 2011. Delay discounting: I'm a k, you're a k. *J Exp Anal Behav* 96, 427-439.
- Oei, N.Y., Rombouts, S.A., Soeter, R.P., van Gerven, J.M., Both, S., 2012a. Dopamine modulates reward system activity during subconscious processing of sexual stimuli. *Neuropsychopharmacology* 37, 1729-1737.
- Oldershaw, A., Grima, E., Jollant, F., Richards, C., Simic, M., Taylor, L., Schmidt, U., 2009. Decision making and problem solving in adolescents who deliberately self-harm. *Psychol Med* 39, 95-104.
- Olds, J., 1958. Self-Stimulation Of The Brain - Its Use To Study Local Effects Of Hunger, Sex, And Drugs. *Science* 127, 315-324.
- Olie, E., Ding, Y., Le Bars, E., de Champfleury, N.M., Mura, T., Bonafe, A., Courtet, P., Jollant, F., 2015. Processing of decision-making and social threat in patients with history of suicidal attempt: A neuroimaging replication study. *Psychiatry Res* 234, 369-377.
- Olino, T.M., McMakin, D.L., Morgan, J.K., Silk, J.S., Birmaher, B., Axelson, D.A., Williamson, D.E., Dahl, R.E., Ryan, N.D., Forbes, E.E., 2014. Reduced reward anticipation in youth at high-risk for unipolar depression: A preliminary study. *Developmental Cognitive Neuroscience* 8, 55-64.

- Opbroek, A., Delgado, P.L., Laukes, C., McGahuey, C., Katsanis, J., Moreno, F.A., Manber, R., 2002. Emotional blunting associated with SSRI-induced sexual dysfunction. Do SSRIs inhibit emotional responses? *International Journal of Neuropsychopharmacology* 5, 147-151.
- Ossewaarde, L., Verkes, R.J., Hermans, E.J., Kooijman, S.C., Uner, M., Tendolkar, I., van Wingen, G.A., Fernandez, G., 2011. Two-Week Administration of the Combined Serotonin-Noradrenaline Reuptake Inhibitor Duloxetine Augments Functioning of Mesolimbic Incentive Processing Circuits. *Biological Psychiatry* 70, 568-574.
- Oswald, L.M., Wand, G.S., Wong, D.F., Brown, C.H., Kuwabara, H., Brasic, J.R., 2015. Risky decision-making and ventral striatal dopamine responses to amphetamine: a positron emission tomography [(11)C]raclopride study in healthy adults. *Neuroimage* 113, 26-36.
- Ott, T., Jacob, S.N., Nieder, A., 2014. Dopamine Receptors Differentially Enhance Rule Coding in Primate Prefrontal Cortex Neurons. *Neuron* 84, 1317-1328.
- Palmiter, S., Justo, D., Jauffret, C., Pavlicek, B., Dauta, A., Delmaire, C., Czernecki, V., Karachi, C., Capelle, L., Durr, A., Pessiglione, M., 2012. Critical Roles for Anterior Insula and Dorsal Striatum in Punishment-Based Avoidance Learning. *Neuron* 76, 998-1009.
- Pan, P.M., Sato, J.R., Salum, G.A., Rohde, L.A., Gadelha, A., Zugman, A., Mari, J., Jackowski, A., Picon, F., Miguel, E.C., Pine, D.S., Leibenluft, E., Bressan, R.A., Stringaris, A., 2017. Ventral Striatum Functional Connectivity as a Predictor of Adolescent Depressive Disorder in a Longitudinal Community-Based Sample. *American Journal of Psychiatry* 174, 1112-1119.
- Papageorgiou, C., Wells, A., 2003. An empirical test of a clinical metacognitive model of rumination and depression. *Cognitive Therapy and Research* 27, 261-273.
- Parent, A., Hazrati, L.N., Charara, A., 1997. The striatopallidal fiber system in primates. *Advances in Neurology*, Volume 74 74, 19-29.
- Parkes, L.M., Rashid, W., Chard, D.T., Tofts, P.S., 2004. Normal cerebral perfusion measurements using arterial spin labeling: reproducibility, stability, and age and gender effects. *Magnetic Resonance in Medicine* 51, 736-743.

- Paulus, M.P., Rogalsky, C., Simmons, A., Feinstein, J.S., Stein, M.B., 2003. Increased activation in the right insula during risk-taking decision making is related to harm avoidance and neuroticism. *NeuroImage* 19, 1439-1448.
- Payer, D.E., Baicy, K., Lieberman, M.D., London, E.D., 2012. Overlapping Neural Substrates Between Intentional and Incidental Down-Regulation of Negative Emotions. *Emotion* 12, 229-235.
- Paykel, E.S., Priest, R.G., 1992. Recognition And Management Of Depression In General-Practice - Consensus Statement. *British Medical Journal* 305, 1198-1202.
- Pessiglione, M., Czernecki, V., Pillon, B., Dubois, B., Schüpbach, M., Agid, Y., Tremblay, L., 2005. An Effect of Dopamine Depletion on Decision-making: The Temporal Coupling of Deliberation and Execution. *J Cogn Neurosci* 17, 1886-1896.
- Pessiglione, M., Seymour, B., Flandin, G., Dolan, R.J., Frith, C.D., 2006. Dopamine-dependent prediction errors underpin reward-seeking behaviour in humans. *Nature* 442, 1042.
- Phan, K.L., Fitzgerald, D.A., Nathan, P.J., Moore, G.J., Uhde, T.W., Tancer, M.E., 2005. Neural substrates for voluntary suppression of negative affect: A functional magnetic resonance imaging study. *Biological Psychiatry* 57, 210-219.
- Phillips, M., 2013. Neural circuitry supporting reward processing in adult bipolar disorder: categorical and dimensional perspectives. *Bipolar Disorders* 15, 26-27.
- Pine, A., Shiner, T., Seymour, B., Dolan, R.J., 2010. Dopamine, time, and impulsivity in humans. *J Neurosci* 30, 8888-8896.
- Pizzagalli, D.A., Evins, A.E., Schetter, E.C., Frank, M.J., Pajtas, P.E., Santesso, D.L., Culhane, M., 2008a. Single dose of a dopamine agonist impairs reinforcement learning in humans: behavioral evidence from a laboratory-based measure of reward responsiveness. *Psychopharmacology (Berl)* 196, 221-232.

- Pizzagalli, D.A., Goetz, E., Ostacher, M., Iosifescu, D.V., Perlis, R.H., 2008b. Euthymic patients with bipolar disorder show decreased reward learning in a probabilistic reward task. *Biological Psychiatry* 64, 162-168.
- Pizzagalli, D.A., Holmes, A.J., Dillon, D.G., Goetz, E.L., Birk, J.L., Bogdan, R., Dougherty, D.D., Iosifescu, D.V., Rauch, S.L., Fava, M., 2009a. Reduced caudate and nucleus accumbens response to rewards in unmedicated individuals with major depressive disorder. *Am J Psychiatry* 166, 702-710.
- Pizzagalli, D.A., Iosifescu, D., Hallett, L.A., Ratner, K.G., Fava, M., 2008c. Reduced hedonic capacity in major depressive disorder: Evidence from a probabilistic reward task. *Journal of Psychiatric Research* 43, 76-87.
- Pizzagalli, D.A., Jahn, A.L., O'Shea, J.P., 2005. Toward an objective characterization of an anhedonic phenotype: A signal detection approach. *Biological Psychiatry* 57, 319-327.
- Pleger, B., Ruff, C.C., Blankenburg, F., Kloppel, S., Driver, J., Dolan, R.J., 2009a. Influence of dopaminergically mediated reward on somatosensory decision-making. *PLoS Biol* 7, e1000164.
- Plichta, M.M., Schwarz, A.J., Grimm, O., Morgen, K., Mier, D., Haddad, L., Gerdes, A.B.M., Sauer, C., Tost, H., Esslinger, C., Colman, P., Wilson, F., Kirsch, P., Meyer-Lindenberg, A., 2012. Test-retest reliability of evoked BOLD signals from a cognitive-emotive fMRI test battery. *NeuroImage* 60, 1746-1758.
- Plomin, R., Haworth, C.M.A., Davis, O.S.P., 2009. Common disorders are quantitative traits. *Nature Reviews Genetics* 10, 872-878.
- Pohlack, S.T., Nees, F., Ruttorf, M., Schad, L.R., Flor, H., 2012. Activation of the ventral striatum during aversive contextual conditioning in humans. *Biological Psychology* 91, 74-80.
- Poldrack, R.A., Mumford, J.A., Nichols, T.E., 2011. *Handbook of Functional MRI Data Analysis*. Cambridge University Press.
- Price, J., Cole, V., Goodwin, G.M., 2009. Emotional side-effects of selective serotonin reuptake inhibitors: qualitative study. *British Journal of Psychiatry* 195, 211-217.

- Pringle, A., Browning, M., Cowen, P.J., Harmer, C.J., 2011. A cognitive neuropsychological model of antidepressant drug action. *Progress in Neuro-Psychopharmacology & Biological Psychiatry* 35, 1586-1592.
- Proudfit, G.H., 2015. The reward positivity: From basic research on reward to a biomarker for depression. *Psychophysiology* 52, 449-459.
- Pulcu, E., Trotter, P.D., Thomas, E.J., McFarquhar, M., Juhasz, G., Sahakian, B.J., Deakin, J.F., Zahn, R., Anderson, I.M., Elliott, R., 2014. Temporal discounting in major depressive disorder. *Psychol Med* 44, 1825-1834.
- Quevedo, K., Ng, R., Scott, H., Kodavaganti, S., Smyda, G., Diwadkar, V., Phillips, M., 2017. Ventral Striatum Functional Connectivity during Rewards and Losses and Symptomatology in Depressed Patients. *Biological Psychology* 123, 62-73.
- Rapaport, M.H., Judd, L.L., Schettler, P.J., Yonkers, K.A., Thase, M.E., Kupfer, D.J., Frank, E., Plewes, J.M., Tollefson, G.D., Rush, A.J., 2002. A descriptive analysis of minor depression. *American Journal of Psychiatry* 159, 637-643.
- Rawal, A., Collishaw, S., Thapar, A., Rice, F., 2013. A Direct Method of Assessing Underlying Cognitive Risk for Adolescent Depression. *Journal of Abnormal Child Psychology* 41, 1279-1288.
- Rawlings, N.B., Norbury, R., Cowen, P.J., Harmer, C.J., 2010. A single dose of mirtazapine modulates neural responses to emotional faces in healthy people. *Psychopharmacology* 212, 625-634.
- Rehm, L.P., 1978. Mood, Pleasant Events, And Unpleasant Events - 2 Pilot-Studies. *Journal of Consulting and Clinical Psychology* 46, 854-859.
- Remijnse, P.L., Nielen, M.M., van Balkom, A.J., Hendriks, G.J., Hoogendijk, W.J., Uylings, H.B., Veltman, D.J., 2009. Differential frontal-striatal and paralimbic activity during reversal learning in major depressive disorder and obsessive-compulsive disorder. *Psychol Med* 39, 1503-1518.
- Rice, F., Rawal, A., Riglin, L., Lewis, G., Dunsmuir, S., 2015. Examining reward-seeking, negative self-beliefs and over-general autobiographical memory as mechanisms of change in classroom prevention programs for adolescent depression. *Journal of Affective Disorders* 186, 320-327.

- Richards, D.A., Ekers, D., McMillan, D., Taylor, R.S., Byford, S., Warren, F.C., Barrett, B., Farrand, P.A., Gilbody, S., Kuyken, W., O'Mahen, H., Watkins, E.R., Wright, K.A., Hollon, S.D., Reed, N., Rhodes, S., Fletcher, E., Finning, K., 2016. Cost and Outcome of Behavioural Activation versus Cognitive Behavioural Therapy for Depression (COBRA): a randomised, controlled, non-inferiority trial. *Lancet* 388, 871-880.
- Richards, J.M., Plate, R.C., Ernst, M., 2013. A Systematic Review of fMRI Reward Paradigms in Adolescents versus Adults: The Impact of Task Design and Implications for Understanding Neurodevelopment. *Neurosci Biobehav Rev* 37.
- Rizvi, Pizzagalli, D.A., Sproule, B.A., Kennedy, S.H., 2016. Assessing anhedonia in depression: Potentials and pitfalls. *Neuroscience & Biobehavioral Reviews* 65, 21-35.
- Rizvi, Quilty, L.C., Sproule, B.A., Cyriac, A., Bagby, R.M., Kennedy, S.H., 2015. Development and validation of the Dimensional Anhedonia Rating Scale (DARS) in a community sample and individuals with major depression. *Psychiatry Research* 229, 109-119.
- Robinson, O.J., Standing, H.R., DeVito, E.E., Cools, R., Sahakian, B.J., 2010. Dopamine precursor depletion improves punishment prediction during reversal learning in healthy females but not males. *Psychopharmacology (Berl)* 211, 187-195.
- Rock, P.L., Harmer, C.J., McTavish, S.F.B., Goodwin, G.M., Rogers, R.D., 2013. Short-Term Quetiapine Treatment Alters the Use of Reinforcement Signals during Risky Decision-Making and Promotes the Choice of Negative Expected Values in Healthy Adult Males. *Journal of Neuroscience* 33, 15588-15595.
- Roiser, J.P., Elliott, R., Sahakian, B.J., 2012. Cognitive Mechanisms of Treatment in Depression. *Neuropsychopharmacology* 37, 117-136.
- Roiser, J.P., McLean, A., Ogilvie, A.D., Blackwell, A.D., Bamber, D.J., Goodyer, I., Jones, P.B., Sahakian, B.J., 2005. The subjective and cognitive effects of acute phenylalanine and tyrosine depletion in patients recovered from depression. *Neuropsychopharmacology* 30, 775-785.

- Rolls, E.T., 1989. Information-Processing In The Taste System Of Primates. *Journal of Experimental Biology* 146, 141-164.
- Rolls, E.T., 2000. The orbitofrontal cortex and reward. *Cerebral Cortex* 10, 284-294.
- Rolls, E.T., 2016. Reward Systems in the Brain and Nutrition. In: Stover, P.J. (Ed.), *Annual Review of Nutrition*, Vol 36. Annual Reviews, Palo Alto, pp. 435-470.
- Rose, G., Barker, D.J., 1978. Epidemiology for the uninitiated. What is a case? Dichotomy or continuum? *British Medical Journal* 2, 873.
- Rosenkranz, J.A., Grace, A.A., 2002. Cellular mechanisms of infralimbic and prelimbic prefrontal cortical inhibition and dopaminergic modulation of basolateral amygdala neurons in vivo. *Journal of Neuroscience* 22, 324-337.
- Ross, S.B., Renyi, A.L., 1969. Inhibition Of Uptake Of Tritiated 5-Hydroxytryptamine In Brain Tissue. *European Journal of Pharmacology* 7, 270-278.
- Rothkirch, M., Tonn, J., Koehler, S., Sterzer, P., 2017. Neural mechanisms of reinforcement learning in unmedicated patients with major depressive disorder. *Brain* 140, 1147-1157.
- Rottenberg, J., Kasch, K.L., Gross, J.J., Gotlib, I.H., 2002. Sadness and Amusement Reactivity Differentially Predict Concurrent and Prospective Functioning in Major Depressive Disorder. *Emotion* 2, 135-146.
- Routtenberg, A., Lindy, J., 1965. Effects Of Availability Of Rewarding Septal And Hypothalamic Stimulation On Bar Pressing For Food Under Conditions Of Deprivation. *Journal of Comparative and Physiological Psychology* 60, 158-+.
- Rutledge, R.B., Skandali, N., Dayan, P., Dolan, R.J., 2014. A computational and neural model of momentary subjective well-being. *Proceedings of the National Academy of Sciences of the United States of America* 111, 12252-12257.
- Rutledge, R.B., Skandali, N., Dayan, P., Dolan, R.J., 2015. Dopaminergic Modulation of Decision Making and Subjective Well-Being. *Journal of Neuroscience* 35, 9811-9822.
- Rzepa, E., Fisk, J., McCabe, C., 2017. Blunted neural response to anticipation, effort and consummation of reward and aversion in adolescents with depression symptomatology. *Journal of Psychopharmacology* 31, 303-311.

- Salamone, J.D., Correa, M., 2012. The Mysterious Motivational Functions of Mesolimbic Dopamine. *Neuron* 76, 470-485.
- Salamone, J.D., Cousins, M.S., Bucher, S., 1994. Anhedonia Or Anergia - Effects Of Haloperidol And Nucleus-Accumbens Dopamine Depletion On Instrumental Response Selection In A T-Maze Cost-Benefit Procedure. *Behavioural Brain Research* 65, 221-229.
- Sambrook, T.D., Goslin, J., 2015. A Neural Reward Prediction Error Revealed by a Meta-Analysis of ERPs Using Great Grand Averages. *Psychological Bulletin* 141, 213-235.
- Sanford, M., Dhillon, S., 2015. Lurasidone: A Review of Its Use in Adult Patients with Bipolar I Depression. *CNS Drugs* 29, 253-263.
- Santarelli, L., Saxe, M., Gross, C., Surget, A., Battaglia, F., Dulawa, S., Weisstaub, N., Lee, J., Duman, R., Arancio, O., Belzung, C., Hen, R., 2003. Requirement of hippocampal neurogenesis for the behavioral effects of antidepressants. *Science* 301, 805-809.
- Santesso, D.L., Evins, A.E., Frank, M.J., Schetter, E.C., Bogdan, R., Pizzagalli, D.A., 2009. Single dose of a dopamine agonist impairs reinforcement learning in humans: evidence from event-related potentials and computational modeling of striatal-cortical function. *Hum Brain Mapp* 30, 1963-1976.
- Santesso, D.L., Steele, K.T., Bogdan, R., Holmes, A.J., Deveney, C.M., Meites, T.M., Pizzagalli, D.A., 2008. Enhanced negative feedback responses in remitted depression. *NeuroReport* 19, 1045-1048.
- Satterthwaite, T.D., Vandekar, L., Katchmar, N., Ruparel, K., Elliott, M.A., Baldassano, C., Leibenluft, E., Thase, M.E., Gur, R.C., Gur, R.E., Kable, J.W., Wolf, D.H., 2014. Common and Divergent Reward Responses Associated with Severity of Unipolar and Bipolar Depression. *Biological Psychiatry* 75, 371S-371S.
- Saville, C.W., Lancaster, T.M., Stefanou, M.E., Salunkhe, G., Lourmpa, I., Nadkarni, A., Boehm, S.G., Bender, S., Smyrnis, N., Ettinger, U., Feige, B., Biscaldi, M., Mantripragada, K.K., Linden, D.E., Klein, C., 2014. COMT Val158Met genotype is associated with fluctuations in working memory performance:

- converging evidence from behavioural and single-trial P3b measures. *Neuroimage* 100, 489-497.
- Schiller, C.E., Minkel, J., Smoski, M.J., Dichter, G.S., 2013. Remitted major depression is characterized by reduced prefrontal cortex reactivity to reward loss. *Journal of Affective Disorders* 151, 756-762.
- Schoemaker, H., Claustre, Y., Fage, D., Rouquier, L., Chergui, K., Curet, O., Oblin, A., Gonon, F., Carter, C., Benavides, J., Scatton, B., 1997. Neurochemical characteristics of amisulpride, an atypical dopamine D-2/D-3 receptor antagonist with both presynaptic and limbic selectivity. *Journal of Pharmacology and Experimental Therapeutics* 280, 83-97.
- Scholl, J., Kolling, N., Nelissen, N., Browning, M., Rushworth, M.F.S., Harmer, C.J., 2017. Beyond negative valence: 2-week administration of a serotonergic antidepressant enhances both reward and effort learning signals. *PLoS Biol* 15.
- Schott, B.H., Minuzzi, L., Krebs, R.M., Elmenhorst, D., Lang, M., Winz, O.H., Seidenbecher, C.I., Coenen, H.H., Heinze, H.J., Zilles, K., Duzel, E., Bauer, A., 2008. Mesolimbic Functional Magnetic Resonance Imaging Activations during Reward Anticipation Correlate with Reward-Related Ventral Striatal Dopamine Release. *Journal of Neuroscience* 28, 14311-14319.
- Schultz, W., 1998. Predictive reward signal of dopamine neurons. *Journal of Neurophysiology* 80, 1-27.
- Schultz, W., 2016. Dopamine reward prediction error coding. *Dialogues Clin Neurosci* 18, 23-32.
- Schultz, W., Dayan, P., Montague, P.R., 1997. A neural substrate of prediction and reward. *Science* 275, 1593-1599.
- Schultz, W., Romo, R., 1990. Dopamine Neurons Of The Monkey Midbrain - Contingencies Of Responses To Stimuli Eliciting Immediate Behavioral Reactions. *Journal of Neurophysiology* 63, 607-624.
- Schulz, K.F., Chalmers, I., Altman, D.G., 2002. The landscape and lexicon of blinding in randomized trials. *Ann Intern Med* 136, 254-259.
- Schulz, K.F., Grimes, D.A., 2002. Blinding in randomised trials: hiding who got what. *Lancet* 359, 696-700.

- Segarra, N., Metastasio, A., Ziauddeen, H., Spencer, J., Reinders, N.R., Dudas, R.B., Arrondo, G., Robbins, T.W., Clark, L., Fletcher, P.C., Murray, G.K., 2016. Abnormal Frontostriatal Activity During Unexpected Reward Receipt in Depression and Schizophrenia: Relationship to Anhedonia. *Neuropsychopharmacology* 41, 2001-2010.
- Selemon, L.D., Goldman-Rakic, P.S., 1988. Common Cortical And Subcortical Targets Of The Dorsolateral Prefrontal And Posterior Parietal Cortices In The Rhesus-Monkey - Evidence For A Distributed Neural Network Subserving Spatially Guided Behavior. *Journal of Neuroscience* 8, 4049-4068.
- Seligman, M.E., 1972. Learned Helplessness. *Annual Review of Medicine* 23, 407-&.
- Sesack, S.R., Hawrylak, V.A., Matus, C., Guido, M.A., Levey, A.I., 1998. Dopamine axon varicosities in the prelimbic division of the rat prefrontal cortex exhibit sparse immunoreactivity for the dopamine transporter. *Journal of Neuroscience* 18, 2697-2708.
- Sescousse, G., Caldu, X., Segura, B., Dreher, J.C., 2013. Processing of primary and secondary rewards: A quantitative meta-analysis and review of human functional neuroimaging studies. *Neuroscience and Biobehavioral Reviews* 37, 681-696.
- Seymour, B., O'Doherty, J.P., Dayan, P., Koltzenburg, M., Jones, A.K., Dolan, R.J., Friston, K.J., Frackowiak, R.S., 2004. Temporal difference models describe higher-order learning in humans. *Nature* 429, 664 1476-4687.
- Shahnazian, D., Holroyd, C.B., 2017. Distributed representations of action sequences in anterior cingulate cortex: A recurrent neural network approach. *Psychonomic bulletin & review*.
- Sharp, C., Kim, S., Herman, L., Pane, H., Reuter, T., Strathearn, L., 2014. Major depression in mothers predicts reduced ventral striatum activation in adolescent female offspring with and without depression. *J Abnorm Psychol* 123, 298-309.
- Sheehan, D.V., Lecrubier, Y., Sheehan, K.H., Amorim, P., Janavs, J., Weiller, E., Hergueta, T., Baker, R., Dunbar, G.C., 1998. The Mini-International Neuropsychiatric Interview (MINI): The development and validation of a

- structured diagnostic psychiatric interview for DSM-IV and ICD-10. *Journal of Clinical Psychiatry* 59, 22-33.
- Sheline, Y.I., Mintun, M.A., Barch, D.M., Wilkins, C., Snyder, A.Z., Moerlein, S.M., 2004. Decreased hippocampal 5-HT_{2A} receptor binding in older depressed patients using F-18 altanserin positron emission tomography. *Neuropsychopharmacology* 29, 2235-2241.
- Shiroma, P.R., Thuras, P., Johns, B., Lim, K.O., 2014. Emotion recognition processing as early predictor of response to 8-week citalopram treatment in late-life depression. *International Journal of Geriatric Psychiatry* 29, 1132-1139.
- Shmuel, A., Yacoub, E., Pfeuffer, J., Van de Moortele, P.F., Adriany, G., Hu, X.P., Ugurbil, K., 2002. Sustained negative BOLD, blood flow and oxygen consumption response and its coupling to the positive response in the human brain. *Neuron* 36, 1195-1210.
- Simmons, W.K., Burrows, K., Avery, J.A., Kerr, K.L., Bodurka, J., Savage, C.R., Drevets, W.C., 2016. Depression-Related Increases and Decreases in Appetite: Dissociable Patterns of Aberrant Activity in Reward and Interoceptive Neurocircuitry. *Am J Psychiatry* 173, 418-428.
- Smoski, M.J., Felder, J., Bizzell, J., Green, S.R., Ernst, M., Lynch, T.R., Dichter, G.S., 2009. fMRI of alterations in reward selection, anticipation, and feedback in major depressive disorder. *Journal of Affective Disorders* 118, 69-78.
- Smoski, M.J., Lynch, T.R., Rosenthal, M.Z., Cheavens, J.S., Chapman, A.L., Krishnan, R.R., 2008. Decision-making and risk aversion among depressive adults. *J Behav Ther Exp Psychiatry* 39, 567-576.
- Snaith, R.P., Hamilton, M., Morley, S., Humayan, A., Hargreaves, D., Trigwell, P., 1995. A Scale For The Assessment Of Hedonic Tone - The Snaith-Hamilton Pleasure Scale. *British Journal of Psychiatry* 167, 99-103.
- Spielberger, C.D., Gorsuch, R.L., Lushene, R.E., 1970. Manual for the state-trait anxiety inventory.
- Stahl, S.M., 2013. *Stahl's essential psychopharmacology: neuroscientific basis and practical applications*. Cambridge university press.

- Stahl, S.M., Pradko, J.F., Haight, B.R., Modell, J.G., Rockett, C.B., Learned-Coughlin, S., 2004. A review of the neuropharmacology of bupropion, a dual norepinephrine and dopamine reuptake inhibitor. *Primary Care Companion to the Journal of Clinical Psychiatry* 6, 159.
- Staudinger, M.R., Erk, S., Abler, B., Walter, H., 2009. Cognitive reappraisal modulates expected value and prediction error encoding in the ventral striatum. *NeuroImage* 47, 713-721.
- Steele, J.D., Kumar, P., Ebmeier, K.P., 2007. Blunted response to feedback information in depressive illness. *Brain* 130, 2367-2374.
- Stefanovic, B., Warnking, J.M., Pike, G.B., 2004. Hemodynamic and metabolic responses to neuronal inhibition. *NeuroImage* 22, 771-778.
- Stoy, M., Schlagenhaut, F., Sterzer, P., Bermpohl, F., Haegeler, C., Suchotzki, K., Schmack, K., Wrase, J., Ricken, R., Knutson, B., Adli, M., Bauer, M., Heinz, A., Stroehle, A., 2012a. Hyporeactivity of ventral striatum towards incentive stimuli in unmedicated depressed patients normalizes after treatment with escitalopram. *Journal of Psychopharmacology* 26, 677-688.
- Straub, J., Plener, P.L., Sproeber, N., Sprenger, L., Koelch, M.G., Groen, G., Abler, B., 2015. Neural correlates of successful psychotherapy of depression in adolescents. *Journal of Affective Disorders* 183, 239-246.
- Stringaris, A., Goodman, R., Ferdinando, S., Razdan, V., Muhrer, E., Leibenluft, E., Brotman, M.A., 2012. The Affective Reactivity Index: a concise irritability scale for clinical and research settings. *Journal of Child Psychology and Psychiatry* 53, 1109-1117.
- Stringaris, A., Vidal-Ribas Belil, P., Artiges, E., Lemaitre, H., Gollier-Briant, F., Wolke, S., Vulser, H., Miranda, R., Penttila, J., Struve, M., Fadai, T., Kappel, V., Grimmer, Y., Goodman, R., Poustka, L., Conrod, P., Cattrell, A., Banaschewski, T., Bokde, A.L., Bromberg, U., Buchel, C., Flor, H., Frouin, V., Gallinat, J., Garavan, H., Gowland, P., Heinz, A., Ittermann, B., Nees, F., Papadopoulos, D., Paus, T., Smolka, M.N., Walter, H., Whelan, R., Martinot, J.L., Schumann, G., Paillere-Martinot, M.L., Consortium, I., 2015c. The Brain's Response to Reward Anticipation and Depression in Adolescence:

- Dimensionality, Specificity, and Longitudinal Predictions in a Community-Based Sample. *Am J Psychiatry* 172, 1215-1223.
- Strober, M., Green, J., Carlson, G., 1981. Utility Of The Beck Depression Inventory With Psychiatrically Hospitalized Adolescents. *Journal of Consulting and Clinical Psychology* 49, 482-483.
- Sugrue, M.F., 1983. Chronic Anti-Depressant Therapy And Associated Changes In Central Mono-Aminergic Receptor Functioning. *Pharmacol Ther* 21, 1-33.
- Suhara, T., Nakayama, K., Inoue, O., Fukuda, H., Shimizu, M., Mori, A., Tateno, Y., 1992. D1 Dopamine Receptor-Binding In Mood Disorders Measured By Positron Emission Tomography. *Psychopharmacology* 106, 14-18.
- Sulzer, J., Sitaram, R., Blefari, M.L., Kollias, S., Birbaumer, N., Stephan, K.E., Luft, A., Gassert, R., 2013. Neurofeedback-mediated self-regulation of the dopaminergic midbrain. *NeuroImage* 83, 817-825.
- Suppes, T., Datto, C., Minkwitz, M., Nordenhem, A., Walker, C., Darko, D., 2014. Effectiveness of the extended release formulation of quetiapine as monotherapy for the treatment of acute bipolar depression (vol 121, pg 106, 2009). *Journal of Affective Disorders* 168, 484-484.
- Suppes, T., Kroger, H., Pikalov, A., Loebel, A., 2016a. Lurasidone adjunctive with lithium or valproate for bipolar depression: A placebo-controlled trial utilizing prospective and retrospective enrolment cohorts. *Journal of Psychiatric Research* 78, 86-93.
- Suppes, T., Silva, R., Cucchiaro, J., Mao, Y., Targum, S., Streicher, C., Pikalov, A., Loebel, A., 2016b. Lurasidone for the Treatment of Major Depressive Disorder With Mixed Features: A Randomized, Double-Blind, Placebo-Controlled Study. *American Journal of Psychiatry* 173, 400-407.
- Suttajit, S., Srisurapanont, M., Maneeton, N., Maneeton, B., 2014. Quetiapine for acute bipolar depression: a systematic review and meta-analysis. *Drug Design Development and Therapy* 8, 827-838.
- Sutton, R.S., 1988. Learning to predict by the methods of temporal differences. *Machine learning* 3, 9-44 0885-6125.

- Syed, E.C.J., Grima, L.L., Magill, P.J., Bogacz, R., Brown, P., Walton, M.E., 2016. Action initiation shapes mesolimbic dopamine encoding of future rewards. *Nature Neuroscience* 19, 34 1546-1726.
- Sylvester, C.Y.C., Wager, T.D., Lacey, S.C., Hernandez, L., Nichols, T.E., Smith, E.E., Jonides, J., 2003. Switching attention and resolving interference: fMRI measures of executive functions. *Neuropsychologia* 41, 357-370.
- Taylor, D.M., Cornelius, V., Smith, L., Young, A.H., 2014. Comparative efficacy and acceptability of drug treatments for bipolar depression: a multiple-treatments meta-analysis. *Acta Psychiatrica Scandinavica* 130, 452-469.
- Taylor, M.J., Freemantle, N., Geddes, J.R., Bhagwagar, Z., 2006. Early onset of selective serotonin reuptake inhibitor antidepressant action - Systematic review and meta-analysis. *Archives of General Psychiatry* 63, 1217-1223.
- Telzer, E.H., Fuligni, A.J., Lieberman, M.D., Galvan, A., 2014. Neural sensitivity to eudaimonic and hedonic rewards differentially predict adolescent depressive symptoms over time. *Proc Natl Acad Sci U S A* 111, 6600-6605.
- Thirion, B., Pinel, P., Meriaux, S., Roche, A., Dehaene, S., Poline, J.B., 2007. Analysis of a large fMRI cohort: Statistical and methodological issues for group analyses. *Neuroimage* 35, 105-120.
- Tidey, J.W., Miczek, K.A., 1996. Social defeat stress selectively alters mesocorticolimbic dopamine release: An in vivo microdialysis study. *Brain Research* 721, 140-149.
- Tohen, M., Kanba, S., McIntyre, R.S., Fujikoshi, S., Katagiri, H., 2014. Efficacy of olanzapine monotherapy in the treatment of bipolar depression with mixed features. *Journal of Affective Disorders* 164, 57-62.
- Tohen, M., Vieta, E., Calabrese, J., Ketter, T.A., Sachs, G., Bowden, C., Mitchell, P.B., Centorrino, F., Risser, R., Baker, R.W., Evans, A.R., Beymer, K., Dube, S., Tollefson, G.D., Breier, A., 2003. Efficacy of olanzapine and olanzapine-fluoxetine combination in the treatment of bipolar I depression. *Archives of General Psychiatry* 60, 1079-1088.

- Tranter, R., Bell, D., Gutting, P., Harmer, C., Healy, D., Anderson, I.M., 2009. The effect of serotonergic and noradrenergic antidepressants on face emotion processing in depressed patients. *Journal of Affective Disorders* 118, 87-93.
- Treadway, M.T., 2016. The Neurobiology of Motivational Deficits in Depression-An Update on Candidate Pathomechanisms. *Curr Top Behav Neurosci* 27, 337-355.
- Treadway, M.T., Bossaller, N.A., Shelton, R.C., Zald, D.H., 2012. Effort-Based Decision-Making in Major Depressive Disorder: A Translational Model of Motivational Anhedonia. *Journal of Abnormal Psychology* 121, 553-558.
- Treadway, M.T., Buckholtz, J.W., Schwartzman, A.N., Lambert, W.E., Zald, D.H., 2009a. Worth the 'EEfRT'? The effort expenditure for rewards task as an objective measure of motivation and anhedonia. *PLoS One* 4, e6598.
- Treadway, M.T., Zald, D.H., 2011. Reconsidering anhedonia in depression: Lessons from translational neuroscience. *Neuroscience and Biobehavioral Reviews* 35, 537-555.
- Tremblay, L.K., Naranjo, C.A., Graham, S.J., Herrmann, N., Mayberg, H.S., Hevenor, S., Busto, U.E., 2005. Functional neuroanatomical substrates of altered reward processing in major depressive disorder revealed by a dopaminergic probe. *Archives of General Psychiatry* 62, 1228-1236.
- Uhl, B., Kuehner, C., Kirsch, P., Ruttorf, M., Diener, C., Flor, H., 2015a. Altered neural reward and loss processing and prediction error signalling in depression. *Soc Cogn Affect Neurosci* 10, 1102-1112.
- Uher, R., Farmer, A., Maier, W., Rietschel, M., Hauser, J., Marusic, A., Mors, O., Elkin, A., Williamson, R.J., Schmael, C., Henigsberg, N., Perez, J., Mendlewicz, J., Janzing, J.G.E., Zobel, A., Skibinska, M., Kozel, D., Stamp, A.S., Bajs, M., Placentino, A., Barreto, M., McGuffin, P., Aitchison, K.J., 2008. Measuring depression: comparison and integration of three scales in the GENDEP study. *Psychological Medicine* 38, 289-300.
- Uher, R., Perlis, R.H., Henigsberg, N., Zobel, A., Rietschel, M., Mors, O., Hauser, J., Dernovsek, M.Z., Souery, D., Bajs, M., Maier, W., Aitchison, K.J., Farmer, A., McGuffin, P., 2012. Depression symptom dimensions as predictors of

- antidepressant treatment outcome: replicable evidence for interest-activity symptoms. *Psychological Medicine* 42, 967-980.
- Umemoto, A., Holroyd, C.B., 2016. Exploring individual differences in task switching: Persistence and other personality traits related to anterior cingulate cortex function. *Prog Brain Res* 229, 189-212.
- Usiello, A., Baik, J.H., Rouge-Pont, F., Picetti, R., Dierich, A., LeMeur, M., Piazza, P.V., Borrelli, E., 2000. Distinct functions of the two isoforms of dopamine D2 receptors. *Nature* 408, 199-203.
- van der Schaaf, M.E., van Schouwenburg, M.R., Geurts, D.E., Schellekens, A.F., Buitelaar, J.K., Verkes, R.J., Cools, R., 2014. Establishing the dopamine dependency of human striatal signals during reward and punishment reversal learning. *Cereb Cortex* 24, 633-642.
- Vaughan, R.A., Foster, J.D., 2013. Mechanisms of dopamine transporter regulation in normal and disease states. *Trends Pharmacol Sci* 34, 489-496.
- Vetulani, J., Sulser, F., 1975. Action Of Various Antidepressant Treatments Reduces Reactivity Of Noradrenergic Cyclic Amp-Generating System In Limbic Forebrain. *Nature* 257, 495-496.
- Vita, A., De Peri, L., Deste, G., Barlati, S., Sacchetti, E., 2015. The Effect of Antipsychotic Treatment on Cortical Gray Matter Changes in Schizophrenia: Does the Class Matter? A Meta-analysis and Meta-regression of Longitudinal Magnetic Resonance Imaging Studies. *Biol Psychiatry*.
- Viviani, R., Graf, H., Wieggers, M., Abler, B., 2013. Effects of amisulpride on human resting cerebral perfusion. *Psychopharmacology* 229, 95-103.
- Vrieze, E., Ceccarini, J., Pizzagalli, D.A., Bormans, G., Vandenbulcke, M., Demyttenaere, K., Van Laere, K., Claes, S., 2013a. Measuring extrastriatal dopamine release during a reward learning task. *Hum Brain Mapp* 34, 575-586.
- Vrieze, E., Pizzagalli, D.A., Demyttenaere, K., Hompes, T., Sienaert, P., de Boer, P., Schmidt, M., Claes, S., 2013b. Reduced Reward Learning Predicts Outcome in Major Depressive Disorder. *Biological Psychiatry* 73, 639-645.

- Waechter, T., Lungu, O.V., Liu, T., Willingham, D.T., Ashe, J., 2009. Differential Effect of Reward and Punishment on Procedural Learning. *Journal of Neuroscience* 29, 436-443.
- Walsh, A., Browning, M., Drevets, W., Furey, M., Harmer, C., 2017. Dissociable Temporal Effects of Bupropion on Behavioural Measures of Emotional and Reward Processing in Major Depressive Disorder. *Biological Psychiatry* 81, 353-383.
- Walsh, E., Carl, H., Eisenlohr-Moul, T., Minkel, J., Crowther, A., Moore, T., Gibbs, D., Petty, C., Bizzell, J., Smoski, M.J., Dichter, G.S., 2016. Attenuation of Frontostriatal Connectivity During Reward Processing Predicts Response to Psychotherapy in Major Depressive Disorder. *Neuropsychopharmacology*.
- Walsh, M.M., Anderson, J.R., 2012. Learning from experience: Event-related potential correlates of reward processing, neural adaptation, and behavioral choice. *Neuroscience and Biobehavioral Reviews* 36, 1870-1884.
- Walton, M.E., Croxson, P.L., Behrens, T.E.J., Kennerley, S.W., Rushworth, M.F.S., 2007. Adaptive decision making and value in the anterior cingulate cortex. *NeuroImage* 36, 142-154.
- Wang, Chen, Y.F., Fernandez-Seara, M.A., Detre, J.A., 2011a. Potentials and Challenges for Arterial Spin Labeling in Pharmacological Magnetic Resonance Imaging. *Journal of Pharmacology and Experimental Therapeutics* 337, 359-366.
- Wang, Gorenstein, C., 2013. Psychometric properties of the Beck Depression Inventory-II: a comprehensive review. *Revista Brasileira de Psiquiatria* 35, 416-431.
- Wang, J.J., Li, L., Roc, A.C., Alsop, D.C., Tang, K., Butler, N.S., Schnall, M.D., Detre, J.A., 2004. Reduced susceptibility effects in perfusion fMRI with single-shot spin-echo EPI acquisitions at 1.5 Tesla. *Magnetic Resonance Imaging* 22, 1-7.
- Wang, J.J., Licht, D.J., Jahng, G.H., Liu, C.S., Rubin, J.T., Haselgrove, J., Zimmerman, R.A., Detre, J.A., 2003. Pediatric perfusion imaging using pulsed arterial spin labeling. *Journal of Magnetic Resonance Imaging* 18, 404-413.

- Wang, S.-M., Han, C., Lee, S.-J., Jun, T.-Y., Patkar, A.A., Masand, P.S., Pae, C.-U., 2018. Efficacy of antidepressants: bias in randomized clinical trials and related issues. *Expert Review of Clinical Pharmacology* 11, 15-25.
- Wesolowska, A., Nikiforuk, A., Stachowicz, K., Tatarczynska, E., 2006. Effect of the selective 5-HT₇ receptor antagonist SB 269970 in animal models of anxiety and depression. *Neuropharmacology* 51, 578-586.
- Wesselhoeft, R., Sorensen, M.J., Heiervang, E.R., Bilenberg, N., 2013. Subthreshold depression in children and adolescents - a systematic review. *J Affect Disord* 151, 7-22.
- Westbrook, C., 2009. *MRI at a glance*. Cambridge University Press, Cambridge.
- Westheide, J., Wagner, M., Quednow, B.B., Hoppe, C., Cooper-Mahkorn, D., Strater, B., Maier, W., Kuhn, K.U., 2007. Neuropsychological performance in partly remitted unipolar depressive patients: focus on executive functioning. *Eur Arch Psychiatry Clin Neurosci* 257, 389-395.
- Whitaker, A., Johnson, J., Shaffer, D., Rapoport, J.L., Kalikow, K., Walsh, B.T., Davies, M., Braiman, S., Dolinsky, A., 1990. Uncommon Troubles In Young-People - Prevalence Estimates Of Selected Psychiatric-Disorders In A Nonreferred Adolescent Population. *Archives of General Psychiatry* 47, 487-496.
- Whitton, A.E., Treadway, M.T., Pizzagalli, D.A., 2015. Reward processing dysfunction in major depression, bipolar disorder and schizophrenia. *Current Opinion in Psychiatry* 28, 7-12.
- Wichers, M., Aguilera, M., Kenis, G., Krabbendam, L., Myin-Germeys, I., Jacobs, N., Peeters, F., Derom, C., Vlietinck, R., Mengelers, R., Delespaul, P., van Os, J., 2008. The Catechol-O-Methyl Transferase Val(158)Met Polymorphism and Experience of Reward in the Flow of Daily Life. *Neuropsychopharmacology* 33, 3030-3036.
- Wiles, N.J., Fischer, K., Cowen, P., Nutt, D., Peters, T.J., Lewis, G., White, I.R., 2014. Allowing for non-adherence to treatment in a randomized controlled trial of two antidepressants (citalopram versus reboxetine): an example from the GENPOD trial. *Psychological Medicine* 44, 2855-2866.

- Willner, P., Hale, A.S., Argyropoulos, S., 2005. Dopaminergic mechanism of antidepressant action in depressed patients. *Journal of Affective Disorders* 86, 37-45 165-327.
- Wise, 2006. Role of brain dopamine in food reward and reinforcement. *Philosophical Transactions of the Royal Society B-Biological Sciences* 361, 1149-1158.
- Wise, Tracey, 2006a. The role of fMRI in drug discovery. *Journal of Magnetic Resonance Imaging* 23, 862-876 1522-2586.
- Wise, R.A., 2002. Brain reward circuitry: Insights from unsensed incentives. *Neuron* 36, 229-240.
- Wise, R.A., 2008. Dopamine and Reward: The Anhedonia Hypothesis 30 years on. *Neurotox Res* 14, 169-183.
- Wise, R.G., Harris, A.A., Stone, A.J., Murphy, K., 2013. Measurement of OEF and absolute CMRO₂: MRI-based methods using interleaved and combined hypercapnia and hyperoxia. *NeuroImage* 83, 135-147.
- Wise, R.G., Tracey, I., 2006b. The role of fMRI in drug discovery. *Journal of Magnetic Resonance Imaging* 23, 862-876.
- Wittmann, B.C., D'Esposito, M., 2015. Levodopa administration modulates striatal processing of punishment-associated items in healthy participants. *Psychopharmacology* 232, 135-144.
- Wolf, S., 1950. Effects Of Suggestion And Conditioning On The Action Of Chemical Agents In Human Subjects - The Pharmacology Of Placebos. *Journal of Clinical Investigation* 29, 100-109.
- Worbe, Y., Palminteri, S., Hartmann, A., Vidailhet, M., Lehericy, S., Pessiglione, M., 2011. Reinforcement learning and Gilles de la Tourette syndrome: dissociation of clinical phenotypes and pharmacological treatments. *Archives of General Psychiatry* 68, 1257-1266.
- Wu, C.C., Samanez-Larkin, G.R., Katovich, K., Knutson, B., 2014. Affective traits link to reliable neural markers of incentive anticipation. *NeuroImage* 84, 279-289.

- Yacubian, J., Glascher, J., Schroeder, K., Sommer, T., Braus, D.F., Buchel, C., 2006. Dissociable systems for gain- and loss-related value predictions and errors of prediction in the human brain. *J Neurosci* 26, 9530-9537.
- Yacubian, J., Sommer, T., Schroeder, K., Glascher, J., Braus, D.F., Buechel, C., 2007. Subregions of the ventral striatum show preferential coding of reward magnitude and probability. *NeuroImage* 38, 557-563.
- Yang, Y., Zhong, N., Imamura, K., Lu, S., Li, M., Zhou, H., Li, H., Yang, X., Wan, Z., Wang, G., Hu, B., Li, K., 2016. Task and Resting-State fMRI Reveal Altered Salience Responses to Positive Stimuli in Patients with Major Depressive Disorder. *PLoS ONE* 11, e0155092.
- Yatham, L.N., Goldstein, J.M., Vieta, E., Bowden, C.L., Grunze, H., Post, R.M., Suppes, T., Calabrese, J.R., 2005. Atypical antipsychotics in bipolar depression: Potential mechanisms of action. *Journal of Clinical Psychiatry* 66, 40-48.
- Yatham, L.N., Liddle, P.F., Dennie, J., Shiah, I.S., Adam, M.J., Lane, C.J., Lam, R.W., Ruth, T.J., 1999. Decrease in brain serotonin 2 receptor binding in patients with major depression following desipramine treatment - A positron emission tomography study with fluorine-18-labeled setoperone. *Archives of General Psychiatry* 56, 705-711.
- Yeung, N., Holroyd, C.B., Cohen, J.D., 2005. ERP correlates of feedback and reward processing in the presence and absence of response choice. *Cerebral Cortex* 15, 535-544.
- Yin, H.H., Ostlund, S.B., Balleine, B.W., 2008. Reward-guided learning beyond dopamine in the nucleus accumbens: the integrative functions of cortico-basal ganglia networks. *European Journal of Neuroscience* 28, 1437-1448.
- Yohn, S.E., Collins, S.L., Contreras-Mora, H.M., Errante, E.L., Rowland, M.A., Correa, M., Salamone, J.D., 2016a. Not All Antidepressants Are Created Equal: Differential Effects of Monoamine Uptake Inhibitors on Effort-Related Choice Behavior. *Neuropsychopharmacology* 41, 686-694.
- Yohn, S.E., Errante, E.E., Rosenbloom-Snow, A., Somerville, M., Rowland, M., Tokarski, K., Zafar, N., Correa, M., Salamone, J.D., 2016b. Blockade of

uptake for dopamine, but not norepinephrine or 5-HT, increases selection of high effort instrumental activity: Implications for treatment of effort-related motivational symptoms in psychopathology. *Neuropharmacology* 109, 270-280.

Young, A.M.J., 2004. Increased extracellular dopamine in nucleus accumbens in response to unconditioned and conditioned aversive stimuli: studies using 1 min microdialysis in rats. *J Neurosci Methods* 138, 57-63.

Zack, M., Poulos, C.X., 2007. A D2 antagonist enhances the rewarding and priming effects of a gambling episode in pathological gamblers. *Neuropsychopharmacology* 32, 1678-1686.

Zald, D.H., 2003. The human amygdala and the emotional evaluation of sensory stimuli. *Brain Research Reviews* 41, 88-123.

Zald, D.H., Depue, R.A., 2001. Serotonergic functioning correlates with positive and negative affect in psychiatrically healthy males. *Personality and Individual Differences* 30, 71-86 0191-8869.

Zhang, W.-N., Chang, S.-H., Guo, L.-Y., Zhang, K.-L., Wang, J., 2013. The neural correlates of reward-related processing in major depressive disorder: A meta-analysis of functional magnetic resonance imaging studies. *Journal of Affective Disorders* 151, 531-539.

Zigmond, A.S., Snaith, R.P., 1983. The Hospital Anxiety And Depression Scale. *Acta Psychiatrica Scandinavica* 67, 361-370.

Appendix A.

Literature Review of reward/penalty modulation by antidepressants used in the treatment of depression and dopaminergic modulation of reward/penalty processing.

Data source and search strategy

We searched Pubmed, Scopus, PsychInfo and Web of Science for articles published in English until November 1, 2017 (available in full-text and published in a peer-reviewed journal). Antidepressant drug classes and names were retrieved from evidence-based guidelines for treating depressive illness in Bauer et al., (2007) and Cleare et al., (2015) and then entered into the following search syntax “[NAME OF DRUG] AND (Reward OR Reinforcement)”. These included: selective serotonin reuptake inhibitors (SSRIs) (citalopram, escitalopram, paroxetine, fluoxetine, sertraline); serotonin and noradrenaline reuptake inhibitors (SNRIs) (venlafaxine, duloxetine); selective noradrenaline reuptake inhibitors (NRIs) (reboxetine, maprotiline); tricyclic antidepressants (TCAs) (clomipramine, amitriptyline, imipramine, desipramine, lofepramine); dopamine and noradrenaline reuptake inhibitors (DNRI) (bupropion); dopamine reuptake inhibitor (amphetamines, methylphenidate, modafinil); and dopamine antagonists (quetiapine, aripiprazole, risperidone, olanzapine, amisulpride, lurasidone).

In order to identify dopaminergic drugs that have been used in human experimental studies, we used the following search terms: “Dopamine AND (agonist OR antagonist OR precursor OR transporter OR metabolism) AND Reward. Using the name of the drugs identified from this initial search, we then performed a second search as follows: “[NAME OF DRUG] AND (Reward OR Reinforcement)”. This list included: dopamine antagonists (haloperidol, sulpiride); dopamine precursor depletion (acute phenylalanine and tyrosine depletion, alpha-methyl-para-tyrosine); dopamine synthesis enhancement (L-DOPA); dopamine agonists (bromocriptine, cabergoline,

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pramipexole); dopamine metabolism inhibitors (tolcapone). The reference list of all retrieved articles were also checked to detect any previously missed articles. Duplicated studies were removed using the EndNote (X7) smart group function.

Systematic review

For each study, we recorded the following variables: number of participants, study design, dose, the time between drug administration and task completion, the task paradigm and behavioural/neuroimaging findings. These results are presented in Table 1.8 and core findings are discussed in Section 1.6.3.

Detailed Inclusion and exclusion criteria

Inclusion criteria: Studies were required to provide a measure of depression or anhedonia in people with major depression disorder (MDD), at high-risk of depression (HR) or healthy controls (HC). We only selected studies that measured depression, or depressive symptoms, through questionnaires, structured interviews, or clinical diagnosis. We included studies which were performed in human healthy subjects (even if these were used as controls for clinical samples). In terms of reward paradigms employed, and following the classification described in Richards et al (2013) we included instrumental-reward tasks and decision-making tasks, which require participants to complete an action correctly in order to obtain a reward (or avoid a penalty), being this action linked to the reward/penalty value in a trial by trial level. Hence, we excluded reward paradigms in which rewards/aversive stimuli were presented passively. Either positive (e.g. winning money) or negative (e.g. losing money) reward manipulations were permitted. No age restrictions were applied.

Exclusion criteria: We excluded reviews, meta-analyses, proceedings publications and post-mortem autoradiography studies. Studies were excluded if they lacked a standard measure of depression. We excluded studies that measured depressive symptoms only in patients with another disorder (e.g. bipolar or schizophrenia, etc.), and did not include a depressed group also. This was done because our primary question concerns the effects of depression on reward processing and in the absence of a depressed

control group, drawing inferences about such effects would be impossible. We also excluded studies in which reward processing was measured through non-experimental methods such as self-report measures or questionnaires, or studies inspecting general mood effects. Furthermore, to guard against heterogeneity, we excluded studies in which physical punishment was delivered (e.g. heat, pain, electrical shock, etc.) as these are likely to engage different brain networks to receiving, for example, negative feedback. We also excluded using neuroimaging with no behavioural assessment.

Appendix B

This appendix shows questionnaires used to measure depression severity (BDI-II, Beck's Depression Inventory II (Beck, Steer, Ball, and Ranieri, 1996); anhedonia (SHAPS, Snaith-Hamilton Pleasure Scale (Snaith, Hamilton, Morley, Humayan, Hargreaves, and Trigwell, 1995); DARS, Dimensional Anhedonia Rating Scale (Rizvi et al., 2015)); anxiety (HADS, Hospital Anxiety and Depression Scale (Zigmond and Snaith, 1983) and subjective ratings of state anxiety (STAI-S, State Trait Anxiety Inventory (Spielberger, Gorsuch, and Lushene, 1970)) and sedation (VAS, Visual Analogue Scale (Herbert, Johns, and Doré, 1976).

BDI-II

Instructions: this questionnaire consists of 21 groups of statements. Please read each group of statements carefully, and then pick out the one statement in each group that best describes the way you have been feeling **during the past week**, including today. Click the box beside the statement you have picked. If several statements in the group seem to apply equally well, click next to the highest number for that group. Be sure that you do not choose more than one statement for any group, including Item 16 (Changes in Sleeping Pattern) or Item 18 (Changes in Appetite).

1. Sadness

- ☐ 0 I do not feel sad.
- ☐ 1 I feel sad much of the time.
- ☐ 2 I am sad all of the time.
- ☐ 3 I am so sad or unhappy that I can't stand it.

2. Pessimism

- ☐ 0 I am not discouraged about my future.
- ☐ 1 I feel more discouraged about my future than I used to be.
- ☐ 2 I do not expect things to work out for me.
- ☐ 3 I feel my fortune is hopeless and will get only worse.

3. Past Failure

- ☐ 0 I do not feel like a failure.
- ☐ 1 I have failed more than I should have.
- ☐ 2 As I look back I see a lot of failures.
- ☐ 3 I feel I am a total failure as a person.

4. Loss of Pleasure

- ☐ 0 I get as much pleasure as I ever did from the things I enjoy.
- ☐ 1 I don't enjoy things as much as I used to.
- ☐ 2 I get very little pleasure from the things I used to enjoy.
- ☐ 3 I can't get any pleasure from the things I used to enjoy.

5. Guilty Feelings

- ☐ 0 I don't feel particularly guilty.
- ☐ 1 I feel guilty over many things I have done or should have done.
- ☐ 2 I feel quite guilty most of the time.
- ☐ 3 I feel guilty most of the time.

6. Punishment Feelings

- ☐ 0 I don't feel I am being punished.
- ☐ 1 I feel I may be punished.
- ☐ 2 I expect to be punished.
- ☐ 3 I feel I am being punished.

7. Self-Dislike

- ☐ 0 I feel the same about myself as ever.
- ☐ 1 I have lost confidence in myself.
- ☐ 2 I am disappointed in myself.
- ☐ 3 I dislike myself.

8. Self-Criticisms

- ☐ 0 I don't criticize or blame myself more than usual.
- ☐ 1 I am more critical of myself than I used to be.
- ☐ 2 I criticize myself for all of my faults.
- ☐ 3 I blame myself for everything bad that happens.

9. Suicidal Thoughts or Wishes

- ☐ 0 I don't have any thoughts of killing myself.
- ☐ 1 I have thoughts of killing myself, but I would not carry them out.
- ☐ 2 I would like to kill myself.
- ☐ 3 I would kill myself if I had the chance.

10. Crying

- ☐ 0 I don't cry ~~anymore~~ than I used to.
- ☐ 1 I cry more than I used to.
- ☐ 2 I cry over every little thing.
- ☐ 3 I feel like crying, but I can't.

11. Agitation

- ☐ 0 I am no more restless or would up than usual.
- ☐ 1 I feel more restless or would up than usual.
- ☐ 2 I am so restless or agitated that it's hard to stay still.
- ☐ 3 I am so restless that I have to keep moving or doing something.

12. Loss of Interest

- ☐ 0 I have not lost interest in other people or activities.
- ☐ 1 I am less interested in other people or things than before.
- ☐ 2 I have lost most of my interest in other people or things.
- ☐ 3 It's hard to get interested in anything.

13. Indecisiveness

- ☐ 0 I make decisions about as well as ever.
- ☐ 1 I find it more difficult to make decisions than usual.
- ☐ 2 I have much greater difficulty in making decisions than usual.
- ☐ 3 I have trouble making any decision.

14. Worthlessness

- ☐ 0 I do not feel I am worthless.
- ☐ 1 I don't consider myself as worthwhile and useful as I used to.
- ☐ 2 I feel more worthless as compared to other people.
- ☐ 3 I feel utterly worthless.

15. Loss of Energy

- ☐ 0 I have as much energy as ever.
- ☐ 1 I have less energy than I used to have.
- ☐ 2 I don't have enough energy to do very much.
- ☐ 3 I don't have enough energy to do anything.

16. Changes in Sleeping Patterns

- ☐ 0 I have not experienced any change in my sleeping pattern.
- ☐ 1a I sleep somewhat more than usual.
- ☐ 1b I sleep somewhat less than usual.
- ☐ 2a I sleep a lot more than usual.
- ☐ 2b I sleep a lot less than usual.
- ☐ 3a I sleep most of the day.
- ☐ 3b I wake up 1-2 hours early and can't get back to sleep.

17. Irritability

- ☐ 0 I am no more irritable than usual.
- ☐ 1 I am more irritable than usual.
- ☐ 2 I am much more irritable than usual.
- ☐ 3 I am irritable all the time.

18. Changes in Appetite

- ☐ 0 I have not experienced any change in my appetite.
- ☐ 1a My appetite is somewhat less than usual.
- ☐ 1b My appetite is somewhat greater than usual.
- ☐ 2a My appetite is much less than before.
- ☐ 2b My appetite is much greater than usual.
- ☐ 3a I have no appetite at all.
- ☐ 3b I crave food all the time.

19. Concentration Difficulty

- ☐ 0 I can concentrate as well as ever.
- ☐ 1 I can't concentrate as well as usual.
- ☐ 2 It's hard to keep my mind on anything for very long.
- ☐ 3 I find I can't concentrate on anything.

20. Tiredness or Fatigue

- ☐ 0 I am no more tired or fatigued than usual.
- ☐ 1 I get more tired or fatigued more easily than usual.
- ☐ 2 I am too tired or fatigued to do a lot of the things I used to do.
- ☐ 3 I am too tired or fatigued to do most of the things I used to do.

21. Loss of Interest in Sex

- ☐ 0 I have not noticed any recent change in my interest in sex.
- ☐ 1 I am less interested in sex than I used to be.
- ☐ 2 I am much less interested in sex now.
- ☐ 3 I have lost interest in sex completely.

SHAPS

This questionnaire is designed to assess your ability to experience pleasure *in the last few days*. It is important to read each statement very *carefully*. Tick *one* of the boxes ☐ to indicate how much you agree or disagree with each statement.

- 1) I would enjoy my favourite television or radio programme

Strongly disagree	<input type="checkbox"/>
Disagree	<input type="checkbox"/>
Agree	<input type="checkbox"/>
Strongly agree	<input type="checkbox"/>

- 2) I would enjoy being with my family or close friends

Definitely agree	<input type="checkbox"/>
Agree	<input type="checkbox"/>
Disagree	<input type="checkbox"/>
Strongly disagree	<input type="checkbox"/>

- 3) I would find pleasure in my hobbies and pastimes

Strongly disagree	<input type="checkbox"/>
Disagree	<input type="checkbox"/>
Agree	<input type="checkbox"/>
Strongly agree	<input type="checkbox"/>

- 4) I would be able to enjoy my favourite meal

Definitely agree	<input type="checkbox"/>
Agree	<input type="checkbox"/>
Disagree	<input type="checkbox"/>
Strongly disagree	<input type="checkbox"/>

- 5) I would enjoy a warm bath or refreshing shower

Definitely agree	<input type="checkbox"/>
Agree	<input type="checkbox"/>
Disagree	<input type="checkbox"/>
Strongly disagree	<input type="checkbox"/>

- 6) I would find pleasure in the scent of flowers or the smell of a fresh sea breeze or freshly baked bread

Strongly disagree	<input type="checkbox"/>
Disagree	<input type="checkbox"/>
Agree	<input type="checkbox"/>
Strongly agree	<input type="checkbox"/>

- 7) I would enjoy seeing other people's smiling faces

Definitely agree	<input type="checkbox"/>
------------------	--------------------------

Agree ☐
Disagree ☐
Strongly disagree ☐

8) I would enjoy looking smart when I have made an effort with my appearance

Strongly disagree ☐
Disagree ☐
Agree ☐
Strongly agree ☐

9) I would enjoy reading a book, magazine or newspaper

Definitely agree ☐
Agree ☐
Disagree ☐
Strongly disagree ☐

10) I would enjoy a cup of tea or coffee or my favourite drink

Strongly disagree ☐
Disagree ☐
Agree ☐
Strongly agree ☐

11) I would find pleasure in small things, e.g. a bright sunny day, a telephone call from a friend

Strongly disagree ☐
Disagree ☐
Agree ☐
Strongly agree ☐

12) I would be able to enjoy a beautiful landscape or view

Definitely agree ☐
Agree ☐
Disagree ☐
Strongly disagree ☐

13) I would get pleasure from helping others

Strongly disagree ☐
Disagree ☐
Agree ☐
Strongly agree ☐

14) I would feel pleasure when I receive praise from other people

Definitely agree ☐
Agree ☐
Disagree ☐
Strongly disagree ☐

DARS

Instructions: Please think carefully and provide at least 2 examples of pleasurable activities/experiences for each category. **Even if you have not had pleasure from activities/experiences lately, please use the activities/experiences you remember enjoying the most, and answer the questions by how much they apply to you right now.** Check the box that best describes how you feel.

A. Please list at least 2 of your favourite pastimes/hobbies that are NOT primarily social

(Examples: gardening, movies, cooking)

1. _____ 2. _____ 3. _____

Thinking about these activities right now:

	Not at all	Slightly	Moderately	Mostly	Very Much
1. I would enjoy these activities	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
2. I would have a desire to participate in these activities	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
3. I would spend time doing these activities	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
4. I want to do these activities	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
5. These activities would interest me	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
6. These activities would give me pleasure	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
7. I would start these activities without being pushed or encouraged	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
8. I would begin doing them on my own	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
9. I would do them until it was time to stop.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

B. Please list at least 2 of your favourite foods/drinks

(Examples: pizza, coffee)

1. _____ 2. _____ 3. _____

Thinking about these foods/drinks right now:

	Not at all	Slightly	Moderately	Mostly	Very Much
10. I would make an effort to get/make these foods/drinks	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
11. I would enjoy these foods/drinks	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
12. I want to have these foods/drinks	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
13. I would eat as much of these foods as I could	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
14. I would make an effort to eat/drink these foods/drinks	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
15. I would actively try to get these foods/drinks	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

C. Please list at least 2 of your favourite social activities

(Examples: making dinner with partner, meeting friends for coffee)

1. _____ 2. _____ 3. _____

Thinking about these social activities right now:

	Not at all	Slightly	Moderately	Mostly	Very Much
16. Spending time doing these things would make me happy	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
17. I would be interested in doing things that involve other people	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
18. I would be the one to plan these activities	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

19. I would feel cheerful from participating in these social activities	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
20. I would actively participate in these social activities	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
21. I would try to seek out these activities	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

D. Please list at least 2 of your favourite sensory experiences

(Examples: listening to music, watching a sunset, smell of favourite foods, touch)

1. _____ 2. _____ 3. _____

Thinking about these experiences right now:

	Not at all	Slightly	Moderately	Mostly	Very Much
22. I would actively seek out these experiences	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
23. I get excited thinking about these experiences	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
24. If I were to have these experiences I would savor every moment	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
25. I want to have these experiences	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
26. I would make an effort to spend time having these experiences	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Hospital Anxiety and Depression Scale (HADS)

Tick the box beside the reply that is closest to how you have been feeling in the past week. Don't take too long over you replies: your immediate is best.

D	A		D	A	
		I feel tense or "wound up":			I feel as if I am slowed down:
	3 <input type="checkbox"/>	Most of the time	3 <input type="checkbox"/>		Nearly all the time
	2 <input type="checkbox"/>	A lot of the time	2 <input type="checkbox"/>		Very often
	1 <input type="checkbox"/>	From time to time, occasionally	1 <input type="checkbox"/>		Sometimes
	0 <input type="checkbox"/>	Not at all	0 <input type="checkbox"/>		Not at all
		I still enjoy the things I used to enjoy:			I get a sort of frightened feeling like "butterflies" in the stomach:
	0 <input type="checkbox"/>	Definitely as much		0 <input type="checkbox"/>	Not at all
	1 <input type="checkbox"/>	Not quite so much		1 <input type="checkbox"/>	Occasionally
	2 <input type="checkbox"/>	Only a little		2 <input type="checkbox"/>	Quite often
	3 <input type="checkbox"/>	Hardly at all		3 <input type="checkbox"/>	Very often
		I get a sort of frightened feeling as if something awful is about to happen:			I have lost interest in my appearance:
	3 <input type="checkbox"/>	Very definitely and quite badly	3 <input type="checkbox"/>		Definitely
	2 <input type="checkbox"/>	Yes, but not too badly	2 <input type="checkbox"/>		I don't take as much care as I should
	1 <input type="checkbox"/>	A little, but it doesn't worry me	1 <input type="checkbox"/>		I may not take quite as much care
	0 <input type="checkbox"/>	Not at all	0 <input type="checkbox"/>		I take just as much care as ever
		I can laugh and see the funny side of things:			I feel restless as I have to be on the move:
	0 <input type="checkbox"/>	As much as I always could		3 <input type="checkbox"/>	Very much indeed
	1 <input type="checkbox"/>	Not quite so much now		2 <input type="checkbox"/>	Quite a lot
	2 <input type="checkbox"/>	Definitely not so much now		1 <input type="checkbox"/>	Not very much
	3 <input type="checkbox"/>	Not at all		0 <input type="checkbox"/>	Not at all
		Worrying thoughts go through my mind:			I look forward with enjoyment to things:
	3 <input type="checkbox"/>	A great deal of the time	0 <input type="checkbox"/>		As much as I ever did
	2 <input type="checkbox"/>	A lot of the time	1 <input type="checkbox"/>		Rather less than I used to
	1 <input type="checkbox"/>	From time to time, but not too often	2 <input type="checkbox"/>		Definitely less than I used to
	0 <input type="checkbox"/>	Only occasionally	3 <input type="checkbox"/>		Hardly at all

		I feel cheerful:			I get sudden feelings of panic:
3	<input type="checkbox"/>	Not at all		3	<input type="checkbox"/> Very often indeed
2	<input type="checkbox"/>	Not often		2	<input type="checkbox"/> Quite often
1	<input type="checkbox"/>	Sometimes		1	<input type="checkbox"/> Not very often
0	<input type="checkbox"/>	Most of the time		0	<input type="checkbox"/> Not at all
		I can sit at ease and feel relaxed:			I can enjoy a good book or radio or TV program:
	0	<input type="checkbox"/> Definitely	0	<input type="checkbox"/>	Often
	1	<input type="checkbox"/> Usually	1	<input type="checkbox"/>	Sometimes
	2	<input type="checkbox"/> Not often	2	<input type="checkbox"/>	Not often
	3	<input type="checkbox"/> Not at all	3	<input type="checkbox"/>	Very seldom

SELF-EVALUATION QUESTIONNAIRE STAI Form Y-1

DIRECTIONS: A number of statements which people have used to describe themselves are given below. Read each statement and then circle the appropriate number to the right of the statement to indicate how you feel *now*, that is, ***at this moment***. There are no right or wrong answers. Do not spend too much time on any one statement but give the answer which seems to describe your present feelings best.

		MODERATELY SO SOMEWHAT NOT AT ALL	VERY MUCH SO	
1. I feel calm	1	2	3	4
2. I feel secure	1	2	3	4
3. I am tense	1	2	3	4
4. I feel strained	1	2	3	4
5. I feel at ease	1	2	3	4
6. I feel upset	1	2	3	4
7. I am presently worrying over possible misfortunes.....	1	2	3	4
8. I feel satisfied	1	2	3	4
9. I feel frightened.....	1	2	3	4
10. I feel comfortable	1	2	3	4
11. I feel self-confident	1	2	3	4
12. I feel nervous	1	2	3	4
13. I am jittery	1	2	3	4
14. I feel indecisive	1	2	3	4
15. I am relaxed	1	2	3	4
16. I feel content	1	2	3	4
17. I am worried	1	2	3	4
18. I feel confused.....	1	2	3	4
19. I feel steady.....	1	2	3	4
20. I feel pleasant	1	2	3	4

VISUAL ANALOGUE SCALES

This form is a mood rating scale and the intention is to measure your feelings as they are **at this moment**. Please read the following instructions carefully and proceed.

1. Please rate the way you feel in terms of the dimensions given below.
2. Regard the line as representing the full range of each dimension.
3. Rate your feelings as they are **at the moment**.
4. Mark clearly across each line.
5. Do not worry if you are not familiar with the meanings of some of the words, just ask us and we will tell you what they mean.

Alert	_____	Drowsy
Calm	_____	Excited
Strong	_____	Feeble
Muzzy	_____	Clear-headed
Well-coordinated	_____	Clumsy
Lethargic	_____	Energetic
Contented	_____	Discontented
Troubled	_____	Tranquil
Mentally slow	_____	Quick-witted
Tense	_____	Relaxed
Attentive	_____	Dreamy
Incompetent	_____	Proficient
Happy	_____	Sad
Antagonistic	_____	Amicable
Interested	_____	Bored
Withdrawn	_____	Gregarious

Appendix C.

Comparing first level models of the MID task

This appendix follows on from Methods Section 3.8.3.1.

In this thesis, we addressed three questions which are relevant for finding the best model for our version of the MID task:

1. *Are anticipation and feedback regressors highly correlated?* This question is important because the MID task assumes that the anticipation and feedback phase are separate phases or processes. The integrity of the model would be diminished if the two phases were highly correlated.
2. *Are anticipation and feedback regressors highly correlated with the target?* The model of the MID used in this thesis (described above) does not explicitly model the target as we are not interested in the neural correlates of a motor response. However, some studies have included the target in the first level model (e.g. Admon et al., (2017)), and thus it is important to understand whether its inclusion comprises the model via high correlations with the phases occurring before and after the target phase.
3. *Do significant results at the whole-brain level change according to the type of first level model used?* This question is important for testing stability in the findings when different first level design matrices are used.

To address these questions, we used three different first level models. A description of the regressors for each model can be found below.

First level model of the MID	Description and justification of model.
MODEL 1:	This is the model that we used in the thesis (see Figure 3.5).

Target not modelled

Anticipation phase

Anticipation onset = cue onset (start of trial, when cue appears on screen)

Anticipation duration = from cue onset until target onset. (cue onset + variable jitter)

Feedback phase

Feedback onset = when feedback window appears (cue+ variable jitter + max response duration)

Feedback duration = 1450ms

Passive trials:

Passive Cue onset = cue onset (start of trial, when X cue appears on screen)

Duration = 4250ms

Implicit baseline (what is not modelled):

Target = target onset + maximum response duration (700ms).

We did not model the target (the motor response) because (i) we were not interested in the neural activity related to making a motor response and (ii) it has previously been thought to have high collinearity with the anticipation and feedback when modelled explicitly (personal communication).

Blank screen at the end of feedback = The blank screen that occurs after the 1450ms feedback duration to make sure that each 'active' trial lasts 9500ms.

The blank screen has a variable duration. You can argue that feedback is still being processed during the blank screen and should be modelled. However, we decided to not model the blank screen because it provides a time gap between feedback and the subsequent anticipation session. In this way, anticipation and feedback may be at less risk of being collinear.

Movement Regressors – same across all three models

Six rigid-body movement regressors, plus and additional regressor accounting for frame-wise displacement (i.e. the 3D movement from volume 1-2,2-3 etc.), and additional binary regressors to indicate image volumes with spikes greater than 1mm, and images either side of the spike (i.e. motion scrubbing and padding).

MODEL 2:
Target modelled (variable duration) (i.e. the duration of the target changes)

Anticipation, feedback and passive trials have the same onsets and durations as Model 1. The difference with Model 2 is that the target is now explicitly modelled.

Target

Target onset = target onset (following the cue onset + variable jitter)

Target duration = variable (individually titrated) response duration

window according to the tracking algorithm of the task.
We predicted that the strength of the correlations between the anticipation phase and the target, and the feedback phase and the target, would be less if the target duration was variable (i.e. jittered) in line with collinearity principles (Ashburner et al., 2014).

Implicit baseline

Blank screen before feedback = the blank screen time between the target coming off screen and the beginning of feedback.

Blank screen at the end of feedback: (see Model 1 above)

Movement Regressors – same across all three models

**MODEL 3:
Target modelled
(duration fixed at
700 ms)**

Anticipation, feedback and passive trials have same onsets and durations as model 1.

Target

Target onset = target onset (following the cue onset + variable jitter)

Target duration = Fixed at 700 ms (the maximum response duration). This models the time that the target is on screen as well as the blank screen which is displayed before feedback.

Implicit baseline

Blank screen at the end of feedback: (see Model 1 above)

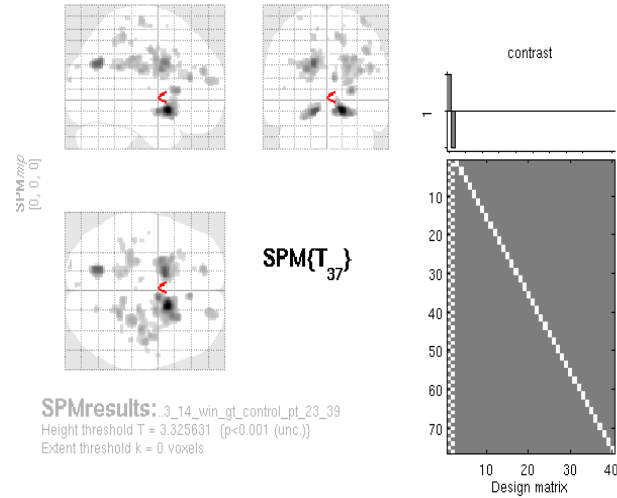
Movement Regressors – same across all three models

In order to address these three questions, we ran each of the first level models for one subject. We tested question 1 by examining the correlation between the anticipation and feedback regressors. We tested question 2 by exploring the correlation between the target and anticipation regressors, and the target and feedback regressors. We tested question 3 by examining whether the results at second level were the same across the three models for the main contrasts of interest: reward anticipation, penalty anticipation, reward feedback, penalty feedback.

In brief, we found that across all three models, there were no correlations greater than ($r = .48$) between individual anticipation, target and feedback regressors and there were no high correlations between the sum of all anticipation regressors with the sum of all feedback regressors ($r = -.11$). Model 3, where the duration of the target was fixed at 700 ms, had similar target-anticipation ($r = 0.43$) and target-feedback correlations ($r = 0.41$) to Model 2 (variable target duration) ($r = 0.42$ and 0.46 respectively).

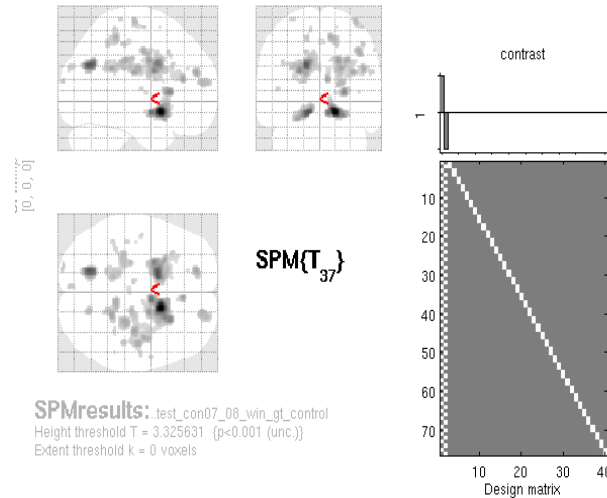
Last of all, we found that significant whole-brain level results remained the same across the three models for all contrasts of interest. We tested the three types of first level design matrix: Model 1 (no target), Model 2 (target variable duration), and Model 3 (target with fixed duration) in a group second-level analysis ($n=39$). As shown in Figure C1 and C2, the results of a paired samples t-test (placebo > lurasidone) for the main contrasts of interest (anticipation win, anticipation loss) did not change according to the model used. Taken together, we concluded that there is a valid distinction between anticipation and feedback phases, that including the target in the model does not increase collinearity, and there is stability in results across different ways of modelling the MID.

Model 1: Target not modelled



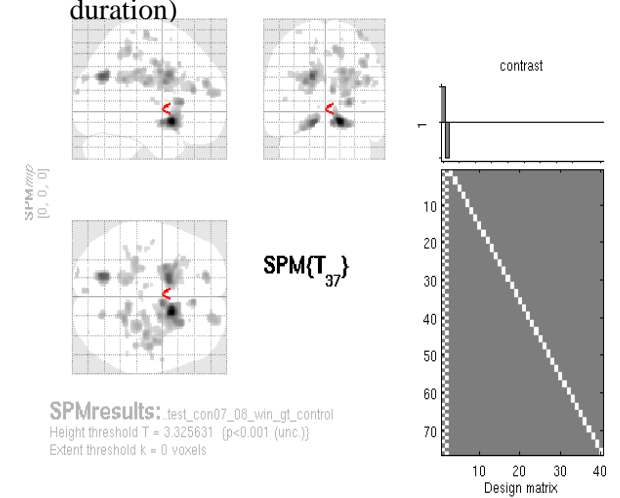
Statistics: <i>p-values adjusted for search volume</i>														
set-level		cluster-level					peak-level				mm mm mm			
D	C	D	PVE-corr	Q	FDR-corr	k _E	D	PVE-corr	Q	FDR-corr	T	(Z _g)	D	uncorr
0,000	39	0,004	0,016	879	0,000		0,002	0,012	6,86	5,48	0,000	15	9	-10
							0,288	0,361	4,96	4,31	0,000	8	-2	-12
							0,060	0,165	5,47	4,66	0,000	-15	4	-12
		0,045	0,048	493	0,005		0,741	0,772	4,23	3,80	0,000	-24	12	-16
							0,976	0,882	3,78	3,45	0,000	-22	-4	-14
		0,266	0,215	253	0,033		0,102	0,208	5,26	4,52	0,000	-16	-66	
		0,008	0,016	748	0,001		0,249	0,368	4,88	4,26	0,000	-15	4	
							0,367	0,441	4,69	4,13	0,000	-24	2	
							0,975	0,882	3,78	3,46	0,000	-18	14	
		0,654	0,443	129	0,114		0,442	0,501	4,59	4,05	0,000	24	18	
		0,958	0,830	45	0,340		0,627	0,761	4,37	3,90	0,000	6	33	
		0,011	0,016	699	0,001		0,711	0,772	4,27	3,82	0,000	18	-3	
							0,754	0,772	4,22	3,79	0,000	34	-20	
							0,851	0,857	4,08	3,69	0,000	45	-15	

Model 2: Target modelled (variable duration)



Statistics: <i>p-values adjusted for search volume</i>													
set-level		cluster-level				peak-level				mm mm mm			
D	C	D PVE-corr	Q FDR-corr	k _E	D uncorr	D PVE-corr	Q FDR-corr	T	(Z _g)	D uncorr			
0,000	42	0,003	0,011	925	0,000	0,001	0,011	6,94	5,52	0,000	15	9	-10
						0,319	0,401	5,04	4,37	0,000	8	-2	-12
		0,031	0,045	537	0,003	0,054	0,191	5,52	4,69	0,000	-15	4	-12
						0,746	0,823	4,24	3,80	0,000	-26	14	-16
						0,978	0,883	3,78	3,45	0,000	-22	-4	-14
		0,215	0,165	277	0,025	0,067	0,191	5,44	4,64	0,000	-16	-68	
		0,006	0,013	792	0,001	0,241	0,457	4,90	4,27	0,000	-15	6	
						0,396	0,523	4,65	4,10	0,000	-24	2	
						0,975	0,883	3,79	3,46	0,000	-18	14	
		0,571	0,367	148	0,089	0,356	0,521	4,71	4,14	0,000	24	18	
		0,230	0,165	268	0,027	0,625	0,823	4,38	3,90	0,000	18	-3	
		0,937	0,718	54	0,291	0,701	0,823	4,29	3,84	0,000	6	33	
		0,040	0,045	502	0,004	0,720	0,823	4,27	3,82	0,000	34	-20	
						0,824	0,850	4,13	3,72	0,000	45	-15	
						0,912	0,854	3,98	3,61	0,000	18	-22	

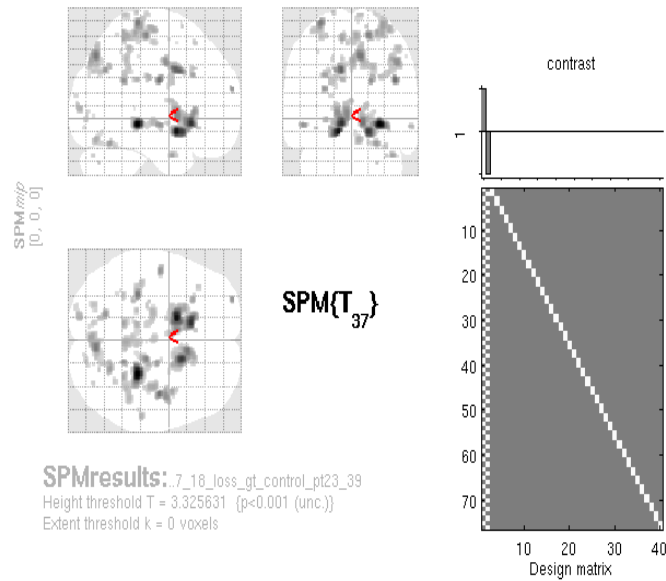
Model 3: Target not modelled (fixed duration)



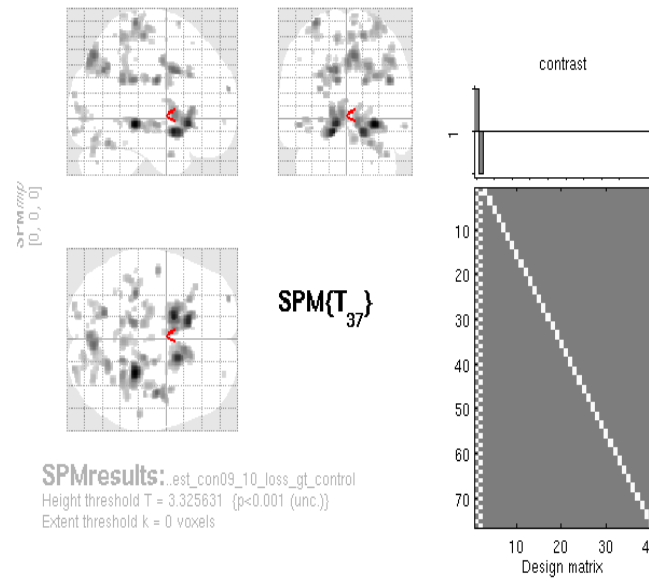
Statistics: <i>p-values adjusted for search volume</i>																	
set-level		cluster-level				peak-level											
D	C	D	PVE-corr	Q	FDR-corr	k _E	D	PVE-corr	Q	FDR-corr	T	(Z _g)	D	uncorr	mm	mm	mm
0,000	50	0,002	0,011	954	0,000	0,001	0,011	6,97	5,54	0,000	15	9 -10					
						0,293	0,519	4,81	4,21	0,000	22	14 -14					
						0,050	0,189	5,56	4,71	0,000	-15	4 -12					
						0,657	0,823	4,34	3,88	0,000	-26	14 -16					
						0,956	0,905	3,87	3,52	0,000	-22	-4 -14					
						0,200	0,178	286	0,023	0,061	0,189	5,46	4,66	0,000	-16	-68	28
						0,005	0,013	817	0,001	0,224	0,457	4,93	4,30	0,000	-15	6	30
										0,369	0,519	4,69	4,13	0,000	-24	2	24
										0,371	0,505	3,81	3,48	0,000	-19	14	26
										0,355	0,519	4,71	4,14	0,000	24	18	6
										0,603	0,823	4,40	3,92	0,000	6	33	16
										0,211	0,178	279	0,025	0,634	18	-3	63
										0,029	0,039	545	0,003	0,680	34	-20	22
										0,802	0,868	4,16	3,75	0,000	45	-15	26
										0,923	0,868	3,96	3,59	0,000	18	-22	34
										0,695	0,823	4,30	3,85	0,000	21	-44	26

Figure C1. Paired –samples t-test (Placebo > Lurasidone) for the contrast of interest: Reward Anticipation

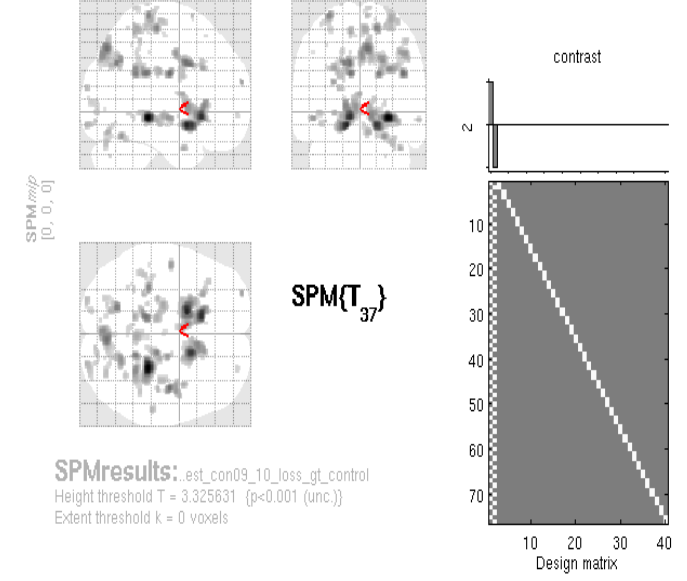
Model 1: Target not modelled



Model 2: Target modelled (variable duration)



Model 3: Target not modelled (fixed duration)



Statistics: p -values adjusted for search volume

set-level		cluster-level				peak-level				mm mm mm		
D	C	$D_{FWE-corr}$	$q_{FDR-corr}$	k_E	D_{uncorr}	$D_{FWE-corr}$	$q_{FDR-corr}$	T	(Z_2)	D_{uncorr}		
0,000	64	0,183	0,277	274	0,019	0,033	0,293	5,76	4,04	0,000	27	-33 -6
		0,004	0,023	775	0,000	0,000	0,293	5,52	4,60	0,000	-15	6 -12
						0,145	0,425	5,17	4,46	0,000	-10	20 -4
						0,770	0,849	4,26	3,02	0,000	-6	6 0
		0,017	0,050	569	0,002	0,170	0,425	5,10	4,41	0,000	15	10 -12
						0,610	0,849	4,44	3,95	0,000	9	16 -4
						0,962	0,849	3,90	3,55	0,000	20	3 -9
		0,207	0,277	260	0,022	0,420	0,849	4,57	4,12	0,000	-12	4 34
						0,996	0,849	3,56	3,56	0,000	-21	2 26
		0,959	0,910	46	0,299	0,572	0,849	4,49	3,99	0,000	42	-10 26
		0,081	0,168	369	0,008	0,639	0,849	4,41	3,93	0,000	8	-74 44
						0,947	0,849	3,95	3,59	0,000	0	-78 40

Statistics: p -values adjusted for search volume

set-level		cluster-level				peak-level				mm mm mm		
D	C	$D_{FWE-corr}$	$q_{FDR-corr}$	k_E	D_{uncorr}	$D_{FWE-corr}$	$q_{FDR-corr}$	T	(Z_2)	D_{uncorr}		
0,000	72	0,087	0,155	362	0,009	0,023	0,243	5,91	4,93	0,000	27	-33 -6
		0,002	0,012	893	0,000	0,000	0,285	5,58	4,72	0,000	-15	6 -12
						0,081	0,285	5,41	4,61	0,000	-12	20 -6
						0,676	0,797	4,37	3,90	0,000	-6	6 2
		0,011	0,025	628	0,001	0,102	0,285	5,32	4,55	0,000	15	10 -12
						0,630	0,797	4,42	3,94	0,000	9	16 -4
						0,996	0,928	3,65	3,35	0,000	12	4 6
		0,886	0,791	70	0,204	0,380	0,797	4,72	4,15	0,000	42	-10 26
		0,004	0,015	758	0,000	0,410	0,797	4,68	4,12	0,000	6	-75 45
						0,662	0,797	4,38	3,91	0,000	0	-78 40
						0,770	0,882	4,25	3,81	0,000	21	-60 36

Statistics: p -values adjusted for search volume

set-level		cluster-level				peak-level				mm mm mm		
D	C	$D_{FWE-corr}$	$q_{FDR-corr}$	k_E	D_{uncorr}	$D_{FWE-corr}$	$q_{FDR-corr}$	T	(Z_2)	D_{uncorr}		
0,000	68	0,086	0,145	365	0,009	0,017	0,162	6,02	5,00	0,000	27	-33 -6
		0,002	0,016	850	0,000	0,000	0,286	5,53	4,69	0,000	-15	6 -12
						0,085	0,286	5,39	4,60	0,000	-12	20 -4
						0,702	0,784	4,33	3,87	0,000	-16	22 2
		0,015	0,032	592	0,001	0,114	0,292	5,27	4,52	0,000	15	10 -12
						0,690	0,784	4,35	3,88	0,000	9	16 -4
						0,998	0,944	3,60	3,31	0,000	12	4 6
		0,911	0,911	63	0,228	0,440	0,784	4,64	4,09	0,000	42	-10 26
		0,185	0,263	275	0,019	0,443	0,784	4,64	4,09	0,000	-12	6 33
						0,991	0,932	3,73	3,41	0,000	-22	2 24
		0,007	0,023	689	0,001	0,449	0,784	4,63	4,09	0,000	6	-75 45
						0,733	0,784	4,30	3,85	0,000	0	-78 40
						0,790	0,784	4,23	3,79	0,000	21	-60 36

Figure C2. Paired –samples t-test (Placebo > Lurasidone) for the contrast of interest: Penalty Anticipation across the three models.

